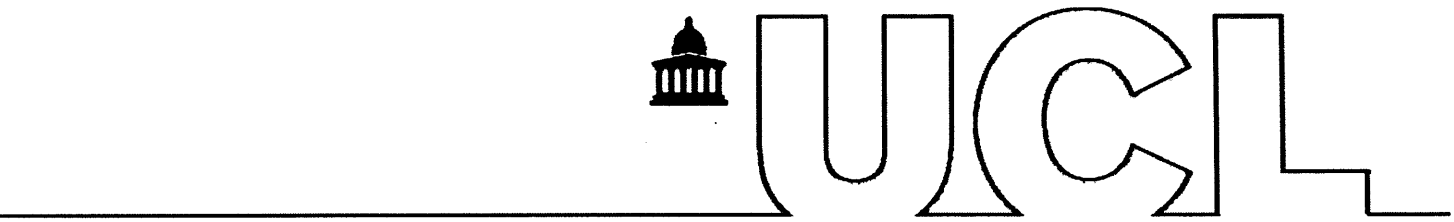

Towards the Synthesis of α-Diazo-β-ketosulfoximines

A Thesis Presented to the University of London in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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ABSTRACT

This thesis presents the work and the methodology undertaken towards the synthesis of α-diazosulfoximines as chiral analogues of α-diazosulfones, as well as the work achieved to investigate novel chemistry for α-diazosulfones.

Towards acyclic α-diazo-β-ketosulfoximines

Sulfoximines proved to have unexpected behaviour during the course of this work in two key-steps. In order to overcome these difficulties, different substrates were targeted and thus, various methods to synthesise acyclic *N*-alkyl, *N*-aryl or *N*-acyl sulfoximines are presented here. Several methods to generate diazo compounds are described, diazo transfer reaction and the use of *N*-nitroso carbamate; attempts to obtain sulfoximine-substituted carbenes through the use of hypervalent iodine(III) were also investigated.

Towards cyclic α-diazo-β-ketosulfoximines

6-Membered ring sulfoximines were targeted and starting from the corresponding sulfoxides, various sulfoximination methods were investigated, as well as their compatibility with other functional groups. A particular attention was given to the relative stereochemistry of substituents and its influence on the behaviour of the substrates during the reactions.

Novel diazosulfones

Previous studies have shown that *C*-silylation of diazoesters expands the scope of chemistry which can be carried out; we therefore aimed to discover if the *C*-silylation of diazosulfones led a similar modification of reactivity. In parallel, we also tried to develop a hybrid of Gilbert-Seyferth reagent, diethyl (diazomethyl)phosphonate, and Julia-Kocienski olefination reagent, 1-phenyl-1*H*-tetrazol-5-yl sulfone, which we expected to behave in a similar way but which could have enhanced reactivity, stability, and ease of use.

To my Grand-Father

and Family

ACKNOWLEDGEMENTS

I would like to thank my supervisor Dr Mike Porter for giving me the chance to work on this ever challenging project. Mike's continual support, encouragement and understanding during my PhD played an invaluable part in the completion of this thesis. I could not have hoped for a more understanding and better advisor for my PhD. I am also grateful to EPSRC, for funding this research project.

I would also like to thank the technical staff at UCL chemistry department especially Dr Abil Aliev for providing the training and assistance with the NMR work, John Hill and Lisa for the mass spectra.

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I want to thank my family for always believing in me, for their love, endless encouragement and support through a lot of phone calls from France!

I would like to thank my friends back in Nice who, during the three years I spent in London, kept coming in my little room to share with me some London adventures!

ABBREVIATIONS

p-ABSA	*Para*-acetamidobenzenesulfonylazide
acac	Acetylacetonyl
Ala	Alanine
app.	Apparent
aq.	Aqueous
atm	Atmosphere
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*Tert*-butyloxycarbonyl
BTEAC	Benzyltriethylammonium chloride
Bus	*Tert*-butylsulfonyl
p-CBSA	*Para*-carboxybenzenesulfonylazide
CI	Chemical ionisation
COD	η^4-Cycloocta-1,5-diene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DIBAL	Di-*iso*-butylaluminium hydride
DIPEA	Di-*iso*-propylethylamine
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMEDA	*N,N'*-Dimethylethylenediamine
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin Periodinane
DMPU	*N,N'*-Dimethylpropylene urea
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
DPEphos	2,2'-Bis(diphenylphosphino)-1,1'-diphenylether
dr.	Diastereomeric ratio
ee.	Enantiomeric excess

EI	Electron impact
eq.	Equivalent
ESI	Electrospray impact
FAB	Fast atom bombardment
GC	Gas Chromatography
h	Hours
Hex	Hexane
KHMDS	Potassium hexamethyldisilazide
L	Ligand
LDA	Lithium diisopropylamide
Leu	Leucine
LHMDS	Lithium hexamethyldisilazide
M	Molar
Mes	Mesityl
min.	Minutes
M.S.	Molecular Sieves
MSH	*O*-Mesitylenesulfonylhydroxylamine
MSHBoc	*O*-Mesitylenesulfonyl-*N*-(*tert*-butyloxycarbonyl)hydroxylamine
NB	[(*p*-Nitrobenzyl)oxy]carbonyl
Nf	Nonafluorobutanesulfonyl
NIS	*N*-Iodosuccinimide
NMO	4-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
Ns	Nosyl, *p*-nitrobenzenesulfonyl
PCC	Pyridinium chlorochromate
PE	Petroleum Ether
PhH	Benzene
Pht	Phthalimide
POM	Pivaloyloxymethyl
PTC	Phase Transfer Catalyst
(*S*)-ptpa	*N*-Phthaloyl-(*S*)-phenylalaninate

PTSA	*p*-Toluenesulfonic acid monohydrate
Py	Pyridine
RT	Room Temperature
sat.	Saturated
Ses	2-Trimethylsilylethanesulfonyl
SM	Starting Material
TBAB	Tetra-*n*-butylammonium bromide
TBAI	Tetra-*n*-butylammonium iodide
TBS	*Tert*-butyldimethylsilyl
TCBoc	2,2,2-Trichloro-1,1-dimethylethoxycarbonyl
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TolBINAP	2,2'-Bis(di-*p*-tolylphosphino)-1,1'-binaphthyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Tri-*iso*propylsilyl
TLC	Thin Layer Chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
Val	Valine

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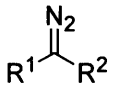
1. Introduction

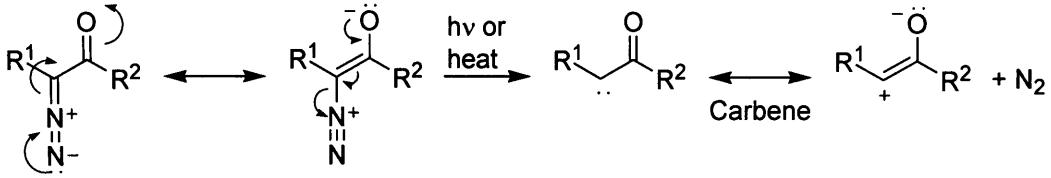
Diazo compounds (Figure 1) find widespread use in organic synthesis.[1]



R^1, R^2= H, alkyl, aryl and functionalised side chains.

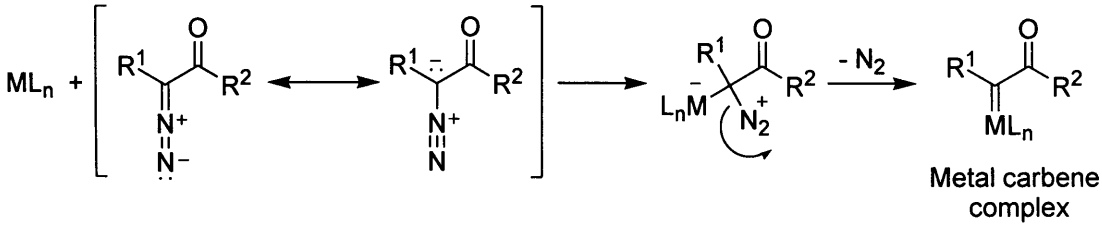
Figure 1

Diazoalkanes such as diazomethane are mild esterification reagents for carboxylic acids. α-Diazocarbonyl compounds, in particular α-diazoketones and α-diazoesters, are commonly used as precursors for the corresponding carbenes (Scheme 1).



Scheme 1: Formation of a free carbene stabilised by the electron-withdrawing effect of the carbonyl group.

Decomposition of α-diazocarbonyl compounds with transition metals such as rhodium(II) or palladium(II) leads to the formation of metal carbene complexes (Scheme 2).

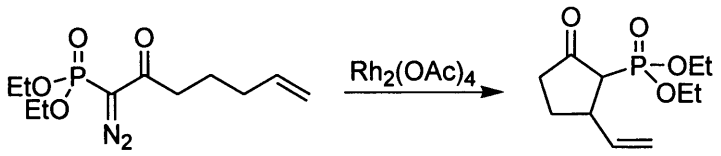


Scheme 2: Formation of a metal carbene complex generated by decomposition of diazo compound with transition metal. M= Metal; L=ligand.

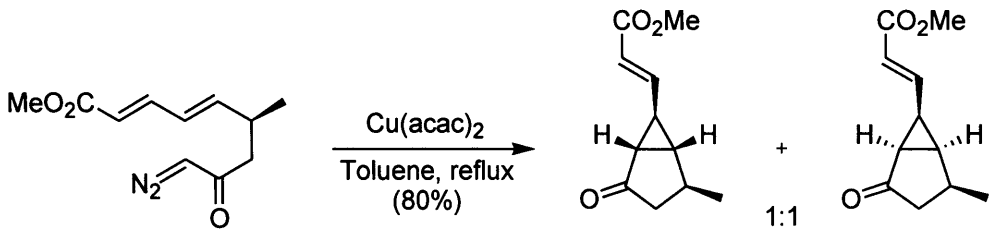
These complexes are similar in reactivity to free carbenes but their reactions usually proceed with greater selectivity. Moreover, the type of metal used to generate carbene complexes can have a strong effect on their chemo- and stereoselectivity. However, only a

few of these highly reactive complexes have been described since they are generally difficult to isolate.[2]

Carbene complexes can undergo a large range of metal-catalysed reactions including C-H, O-H or N-H insertions (Scheme 3) and cyclopropanation of alkenes (Scheme 4)[3].

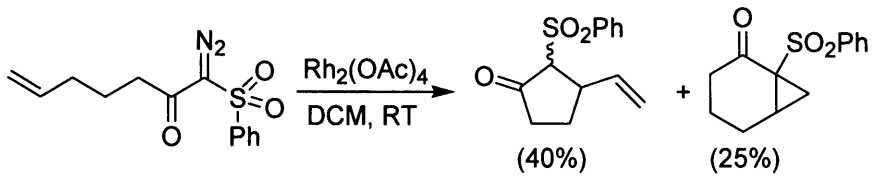


Scheme 3: C-H insertion leading to a 5-membered ring intermediate in the synthesis of the natural product (±)-sarkomycin.[4]



Scheme 4: Decomposition of diazocarbonyl leading to a vinyl cyclopropane ring intermediate in the synthesis of (-)-verbenalol.[3]

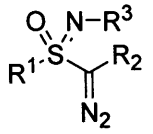
In contrast to α-diazocarbonyl compounds, diazo compounds with electron-withdrawing sulfur substituents have been less extensively exploited. The development of synthetic routes to α-diazosulfones was pioneered by Van Leusen in the 1960s, these compounds undergo the same characteristic reactions as α-diazocarbonyl compounds such as insertions[5] or cyclopropanation[6] (Scheme 5).



Scheme 5: Metal carbene reaction leading to both C-H insertion and cyclopropanation products.

As for α-diazosulfoxides, Venier *et al.* first reported in 1975 the use of phenyl diazomethyl sulfoxide for highly stereoselective cyclopropanation reactions.[7] However these carbene precursors, despite their potential in asymmetric synthesis, were found to be unstable and thus difficult to exploit. Stable α-diazosulfoxides obtained by diazo transfer on the α-position, were first prepared in 1976 by Campbell and Bremner in cephalosporin derivatives,[8] and later Maguire *et al.* reported the synthesis of another series of stable cyclic α-diazosulfoxides.[9]

The aim of this project was first to develop α-diazosulfoximines as chiral analogues of α-diazosulfones and then to test them in a variety of metal carbene reactions. The goal was to obtain synthetically useful levels of diastereoselectivity, which would be induced by the chiral sulfur atom of the sulfoximine moiety (Figure 2).



α-diazosulfoximine
R^1, R^2=H, alkyl, aryl and functionalised side chains
R^3= H, alkyl, vinyl, aryl, SO_2Ar, SO_2R, C(O)OR

Figure 2

1.1. The sulfoximine function

In the late 1940s, several papers were published, all dealing with a toxic factor occurring in many proteins treated with "agene", which is essentially nitrogen trichloride gas. On aging by long storage the baking properties of flour improve, but there are also various chemicals that could be used for this purpose, including agene. However, the treatment of flour with agene produced a toxic factor responsible for great disorder in canine diet.[10, 11]
In a rather tedious procedure Bentley and Whitehead were able to isolate from agenised gluten, after enzymatic digestion and acid hydrolysis, a highly active crystalline material.[12]
The same material was similarly isolated from zein, a corn protein. Bentley showed that only protein relatively rich in methionine became toxic.[13]
This crystalline compound was found to be formally a derivative "*from methionine sulphone by the replacement of O by =NH*", and could clearly contain a asymmetric sulfur

atom.[13, 14] Indeed they were able to separate two diastereomeric forms of the new compound with the new functional group by fractional crystallisation of the corresponding picrates.

The new class of compounds was called *sulphoximide*, following IUPAC convention, but the name *sulphoximine* introduced by Robinson, and now *sulfoximine* is commonly used to designate such compounds.[15]

Structural properties (Figure 3, Table 1)[16]

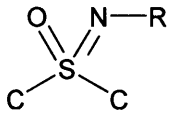


Figure 3

Table 1

Average Bond Angles (°)		*Average Bond Lengths (pm)*	
C-S-C	104.9	C-S	177.2
C-S-O	108.8	S-O	144.4
C-S-N	107.0	S-N	153.7
O-S-N	119.3		

The coordination sphere of the sulfur centre is a slightly distorted tetrahedron with S-N bond lengths (d=153.7 pm) being between typical S-N single bond and triple bond (d=144.1 pm)[17, 18]

The IR spectra of sulfoximines are characterised by two strong absorption bands for the O=S=N unit, for which typical values for stretch vibrations are $\upsilon_{as} \approx 1200$ cm^{-1} and $\upsilon_{s} \approx 1100$ cm^{-1}. For *N*-unsubstituted sulfoximines or "free sulfoximines" in solution, the NH stretch vibration is a band between 3100 and 3400 cm^{-1}.

In ^{1}H NMR spectra, C-bound aliphatic protons in the α-position of the sulfoximidoyl moiety typically resonate in the range of 3.0-3.5 ppm depending on the nature of the *N*-bound substituent. In the ^{13}C NMR spectra, the corresponding C atoms resonate in the 40-50 ppm range.

Due to the amphoteric character of the sulfoximine nitrogen, the acidic protons in the α-position and the potentially stereogenic sulfur atom, sulfoximines promise to be an extremely versatile class of compounds as illustrated in Figure 4.[16]

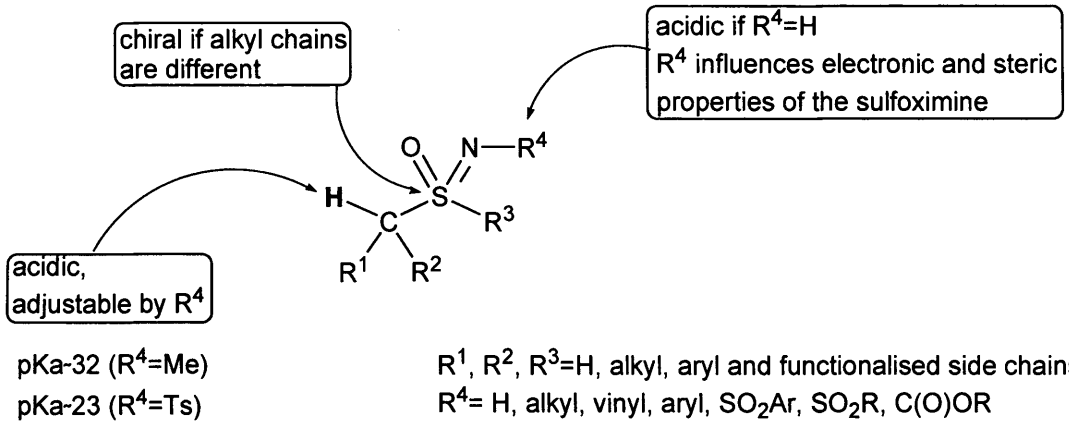


Figure 4: Features of sulfoximidoyl moiety accounting for their unusual chemical versatility.

Added to the reactivity pattern described in Figure 4 the whole unit is electron-withdrawing, which justifies the following classification.[16]

- Sulfoximine as C-nucleophile.

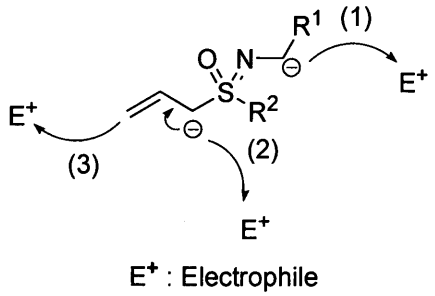


Figure 5: General structure of an allylsulfoximine that can react as C-nucleophile. R^2 is typically an unreactive group (aryl, *t*-Bu).

The reaction can take place at three different nucleophilic sites (Figure 5):

(1) at the negatively polarised carbon adjacent to the nitrogen atom.

(2) at the α-carbon next to the sulfoximine moiety.

(3) at γ-carbon, the vinylogous position.

- Sulfoximine as electrophile.

Two types of reaction are possible in this category:

(1) The sulfoximine moiety remains in the product; Michael additions to vinyl sulfoximine and pericyclic reactions with the sulfoximine being the electron deficient partner (Figure 6).

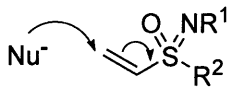


Figure 6: Michael addition on a vinyl sulfoximine.

(2) The sulfoximine moiety acts as a leaving group; typically it is the addition of a nucleophile followed by elimination of the sulfoximine group (Figure 7).

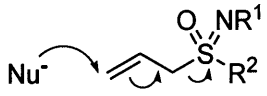


Figure 7: Addition of a nucleophile at the allylic position followed by elimination of the sulfoximine moiety.

Representation of the sulfoximine group:

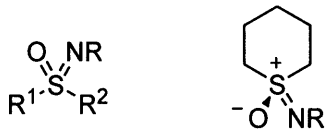


Figure 8

In this thesis, we have chosen to depict differently linear and cyclic sulfoximines as shown in Figure 8. In this project, all the linear sulfoximines used were racemic, and the sulfur atom was the only stereogenic centre; thus the representation of the configuration at this atom is not necessary and the sulfoximines are depicted with S=O and S=N double bonds. As for cyclic sulfoximines, in some cases we obtained mixtures of diastereomers whose relative configuration was determined; for this reason, we have chosen to represent cyclic sulfoximines as the polarised S^+-O^- resonance form shown. This is purely to allow easy

depiction of the relative configuration, and does not reflect any difference in the structure of the sulfoximine moiety in the two cases.

1.2. Synthesis of sulfoximines

1.2.1. Introduction

To access sulfoximines, two main paths have been described. They can be obtained from two classes of non-sulfoximine starting materials, depending on the oxidation state of the central sulfur atom. On the one hand sulfoxides and sulfilimines as sulfur(IV) compounds, on the other hand sulfonimidates and sulfonimidoyl halides, as sulfur(VI) compounds (Figure 9).

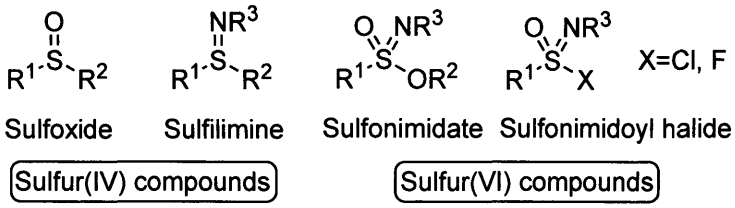
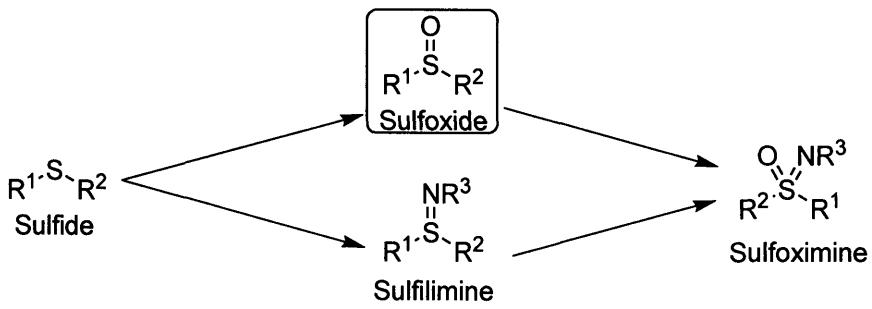


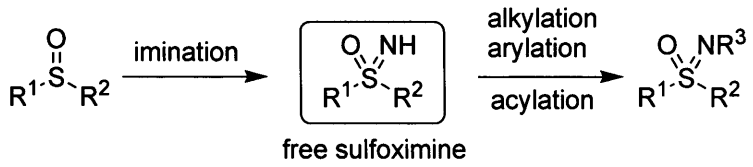
Figure 9

The introduction focuses on the synthesis of sulfoximines from sulfur(IV) compounds, especially methods for the conversion of sulfoxides to sulfoximines (Scheme 6). These methods can also be applied in most cases to the synthesis of sulfilimines from sulfides. Subsequent oxidation of the sulfilimines gives another way to prepare sulfoximines.



Scheme 6

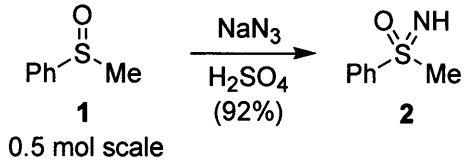
In the past ten years, methods to synthesise sulfoximines via sulfoxides have been greatly improved and a thorough examination of this evolution will be the core of this chapter.
There are two ways to synthesise the sulfoximidoyl moiety from a sulfoxide, either by direct introduction of substituted imine group (R^3=alkyl, aryl, acyl...) or by a two-step sequence (Scheme 7). The latter consists of an imination reaction to synthesise *NH*-sulfoximine followed by derivatisation. This non-substituted intermediate, also called a "free sulfoximine", is a very useful building block and methods of derivatisation have been, rather recently, a field of great investigation in sulfoximine chemistry.



Scheme 7

1.2.2. Classical syntheses of sulfoximines

The oldest method for the oxidative imination of sulfoxides, developed by Johnson,[19, 20] is the action of hydrazoic acid, generated *in situ* by reaction of sodium azide with concentrated sulfuric acid in chloroform. Despite numerous hazards associated with the application of hydrazoic acid, this method is still widely used in large scale synthesis of "free sulfoximine" **2** from methyl phenyl sulfoxide **1** (Scheme 8).

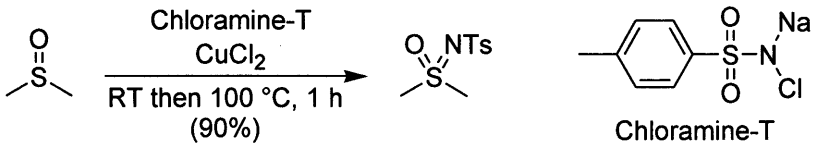


Scheme 8

In addition to the use of a potentially hazardous reagent, this method is limited to sulfoximines having sulfur substituents that can not form stable carbocations; under the acidic reaction conditions, heterolysis of a C-S bond occurs in the case of a tertiary and

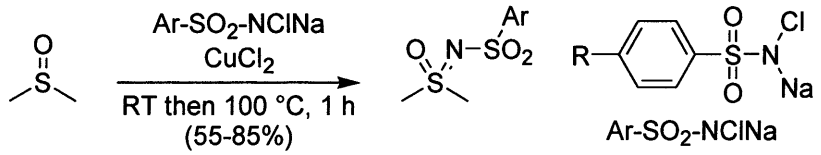
sometimes a secondary alkyl group.[21] Moreover this method leads to partial racemisation of non-racemic sulfoximines during the imination process.

Much more reliable in this respect are reactions involving nitrenes or analogous reactive intermediates, mostly tosyl azide or Chloramine-T (Scheme 9).[21, 22]



Scheme 9

Unfortunately, the use of Chloramine-T was found to be high yielding only in its reaction with DMSO. However, Heintzelman reported later the synthesis of several *N*-sodio-*N*-chlorosulfonamides and their reaction with DMSO in the presence of copper chloride in good yields (Scheme 10, Table 2).[23]

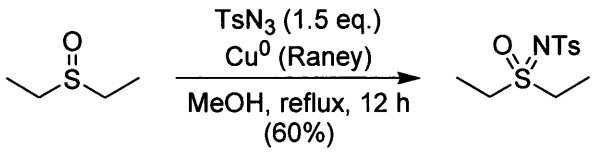


Scheme 10

Table 2

R	Me	H	Cl	NO_2	BnO-CO-NH
Yields (%)	85	78	74	78	55

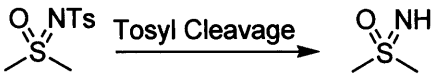
In contrast to the poor reactivity of Chloramine-T with sulfoxides, decomposition of tosyl azide in the presence of copper(0) has proven to be efficient and rather general. This method, discovered in 1967 by Kwart and Khan,[24] can be used to synthesise optically active *N*-tosyl sulfoximines from the corresponding sulfoxides without apparent racemisation. Johnson used this method to prepare several sulfoximines in average to good yield (52-94%) (Scheme 11).[21]



Scheme 11

Although *N*-tosylsulfoximines were useful themselves, it was of interest to be able to obtain *NH* derivatives; however methods available at that point were very dependent on the structure of the sulfoximine and presented several drawbacks in term of toxicity and practicality (Table 3).

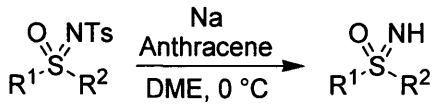
Table 3. Cleavage methods for the tosyl group.

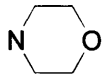


Cleavage method	*Yield (%)*
H_2SO_4 conc.	40
irradiation at 253.7 nm	7
Na/NH_3 liq.	60
Na/Anthracene	93

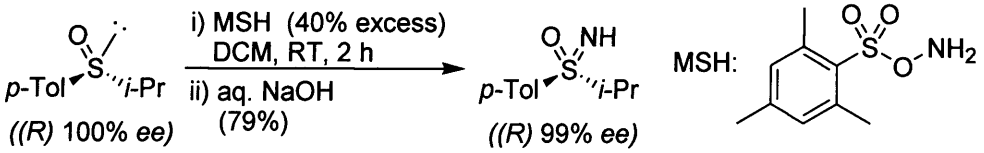
Detosylation using concentrated sulfuric acid[15] leads to partial racemisation and very often to a considerable loss of material (30-40% yield). Reduction using sodium in liquid ammonia gave good results, but because this system is somewhat too powerful a reducing agent, practical difficulties were encountered since exactly two equivalents of sodium had to be used per equivalent of sulfoximine. This problem was overcome by using sodium arenide systems, such as sodium anthracenide in DME developed by Johnson.[25] This method gave high yields of free sulfoximine but only for *S,S*-dialkyl substituted sulfoximines (Table 4).

Table 4: Isolated yields of sulfoximines from reduction of *N*-tosyl sulfoximines with sodium anthracenide in DME.



Entry	R^1	R^2	*Yield (%)*
a	Me	Me	93
b	*t*-Bu	Bu	68
c	*t*-Bu		98
d	Me	CCl_2CH_3	21
e	Ph	Me	0

Still with the goal to obtain *NH*-sulfoximines directly, Tamura *et al.* developed in 1972 a rather flexible method using *O*-mesitylenesulfonylhydroxylamine (MSH) as a nitrene source.[26] Two years later, Johnson[27] synthesised several optically active sulfoximines from optically active sulfoxides with complete retention of configuration (Scheme 12).



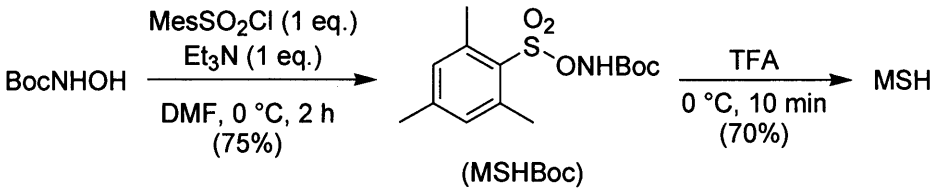
Scheme 12

Treatment of optically active sulfoxides with MSH in DCM for two hours, followed by a basic work-up, afforded the corresponding *NH*-sulfoximines in average yields (60-80%) and high purity (92-100% *ee*).

However, MSH is a problematic reagent, potentially explosive and difficult to synthesise, even with the improved method developed in 1992 by Haga *et al.*[28]

To the original preparation of MSH involving dropwise addition of 70% perchloric acid to a solution of ethyl *O*-(mesitylsulfonyl)acetohydroxamate in dioxane at 0 °C, was preferred a two-step synthesis from commercially available materials. The first step is the reaction of Boc-protected hydroxylamine and mesitylenesulfonyl chloride in the presence of

triethylamine, to synthesise the Boc-protected intermediate (MSHBoc), which treated by TFA, affords MSH as colourless needles in 70% yield (Scheme 13).



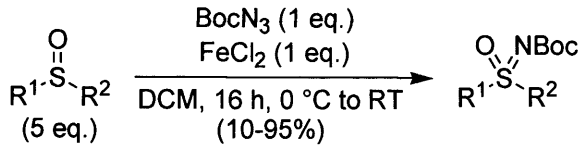
Scheme 13

In conclusion, classical methods for imination reactions of sulfoxides are not general procedures, very often toxic and explosive (MSH procedure, azides), or unsuitable for asymmetric transformations (NaN_3/H_2SO_4); deprotection to access *NH*-sulfoximines is problematic (deprotection of tosyl derivatives harsh or limited to *S,S*-dialkyl sulfoximines). The development of metal-mediated imination reactions was a real improvement regarding the scope of substrates that could be used in such transformations, and more important, methods became safer to carry out.

1.2.3. Metal-mediated imination reactions

1.2.3.1. Iron-promoted and copper-catalysed imination

In view of the various disadvantages of all methods listed previously, the imination procedure involving Boc azide invented in 1998 by Bach[29, 30] was a real improvement despite the fact that this substance is potentially explosive and hazardous to health. The authors described an iron-promoted nitrene transfer from Boc azide to sulfides and sulfoxides (Scheme 14, Table 5).



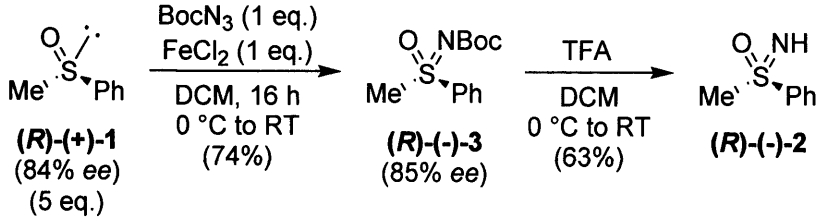
Scheme 14

Table 5

Entry	R^1	R^2	*Yield (%)*
a	Ph	Me	74
b	*i*-Pr	Me	54
c	*t*-Bu	Me	10
d	Bn	Et	95
e	Bn	Ph	40

These results show a relation between the steric hindrance of the sulfoxide and the yield of the sulfoximine (Entries a-c), yields decrease with the increasing size of the substituents attached to the sulfoxide. In the case of *tert*-butyl methyl sulfoxide (Entry c), the bulky *tert*-butyl group apparently strongly hinders an approach of the nitrogen electrophile to the nucleophilic sulfur atom.

Even though the catalytic efficiency of this system is not high and the scope of substrates rather limited, the uneventful deprotection of the Boc-substituted intermediate **3** with TFA, to access useful *NH*-sulfoximine **2**, is the most attractive point of this method (Scheme 15).

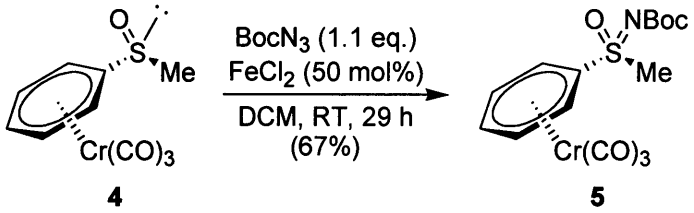


Scheme 15

Investigation of the stereochemical outcome of sulfoxide imination of **(*R*)-(+)-1** (84% *ee*) showed that the reaction was stereospecific, the corresponding sulfoximine **(*R*)-(-)-3** was obtained with 85% ee. After deprotection of the latter, the comparison of the specific

optical rotation with the value reported for **(*S*)-(+)-2**[27] proved that the nitrene transfer had occurred with retention of configuration.
Deprotection using aluminium trichloride/anisole, or alternatively titanium tetrachloride, gave even better results.[16]

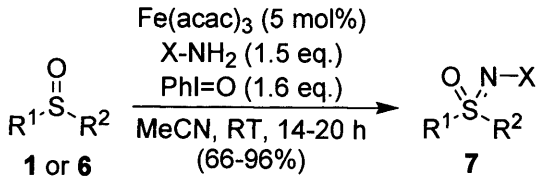
Bolm successfully applied this metal-promoted imination reaction, in a catalytic version, to the synthesis of sulfoximines having benchrotrene skeletons.[31] Decomposition of Boc azide (in slight excess) with iron chloride (0.5 eq.) in the presence of sulfoxide **4** in DCM at room temperature afforded the corresponding sulfoximine **5** in 67% yield.
Simultaneous removal of the chromium moiety and the Boc protecting group, respectively with iodine/air and TFA, followed by GC analysis of the product confirmed that the imination process has been stereospecific (Scheme 16).



4 **5**

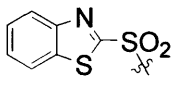
Scheme 16

Regarding iron-mediated imination, Bolm described in 2006 another catalytic system involving this time iron(III) complexes.[32] After optimisation of the reaction conditions, a mixture of iron(III) acetylacetonate (5 mol%), sulfonylamide (1.5 eq.) and iodosylbenzene (1.6 eq.) in acetonitrile at room temperature, was the most efficient combination for the conversion of sulfoxides to sulfoximines (Scheme 17). The examination of the scope of sulfoxides suitable for the imination reaction and sulfonamides that could be used as nitrene-donor species proved that the iron-catalysed protocol is rather general (Table 6).



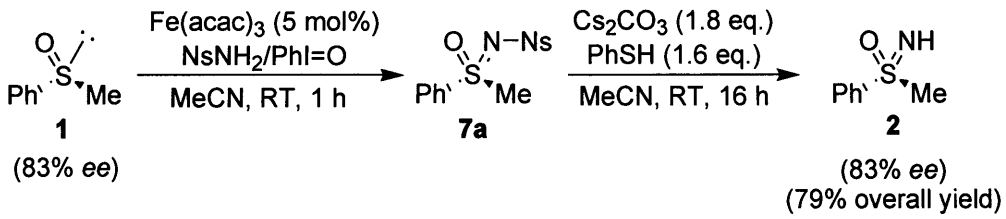
Scheme 17

Table 6

Entry	R^1	R^2	*X*	*SM/Product*	*Yield (%)*
a	Ph	Me	Ns	**1/7a**	96
b	Ph	Me	Ts	**1/7b**	81
c	Ph	Me		**1/7c**	88
d	Ph	Me	Bus	**1/7d**	-
e	Mes	Me	Ns	**6e/7e**	-
f	*t*-Bu	Me	Ns	**6f/7f**	80

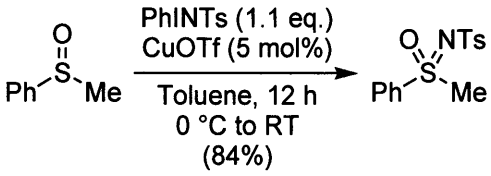
Imination with well-known sulfonamides such as *p*-nitrophenylsulfonylamide (Entry a) or tosylamide (Entry b) readily afforded sulfoximines **7a** and **7b** in good yield (96% and 81% yields respectively), albeit with a longer reaction time for *N*-tosyl sulfoximine (18 h instead of 1 h). More exotic benzothiazolylsulfonylamide (Entry c) also reacts smoothly to give sulfoximine **7c** in 88% yield. However *t*-butylsulfonylamide (Entry d) failed to react due to the bulky *t*-butyl group. Sterically demanding substrates such as mesityl methyl sulfoxide **6e** (Entry e) are not suitable for iron-catalysed imination, even though rather hindered *t*-butyl methyl sulfoxide **6f** (Entry f) was successfully converted to the corresponding sulfoximine **7f** in good yield (80%).

Iron-catalysed imination with *p*-nitrophenylsulfonylamide followed by deprotection of the intermediate **7a** with a mixture of cesium carbonate/thiophenol, converted enantiomerically enriched *(S)*-methyl phenyl sulfoxide **1** (83% *ee*) to the corresponding *NH*-sulfoximine **2** in 79% yield and 83% *ee*. Analysis of the *ee* showed that the two-step sequence proceeds with complete retention of configuration (Scheme 18).



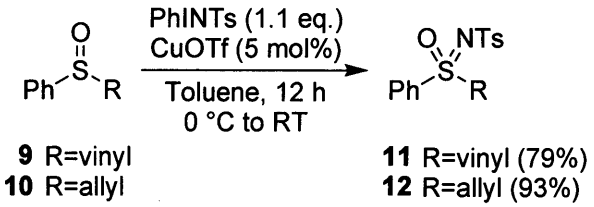
Scheme 18

The combination of metal catalysis and hypervalent iodine(III) species started in 1983 when Groves and Takahashi reported the first aza analogue to epoxidation,[33] followed by the work of Mansuy *et al.* in 1984 who studied the aziridination of alkenes with *N*-tosyliminophenyliodinane (PhINTs) in the presence of iron- or manganese-porphyrins.[34]
Fifteen years ago Evans *et al.*[35] discovered that low-valent copper complexes could catalyse aziridination of various olefins with PhINTs and had made copper salts the catalysts of choice for this reaction. Later Li *et al.*[36] developed an asymmetric version of this aziridination reaction and reported a first fully detailed procedure. In 1996 Uemura[37] applied this methodology with the aim to find a new synthesis of chiral sulfilimines and successfully obtained several of them.
Two years later, Muller[38] reported a new copper-catalysed imination procedure, a very efficient decomposition of hypervalent iodine or iodine(III) species in the presence of a copper(I) salt. Following Uemura's procedure, Muller and Vogt described the synthesis of several *N*-tosyl sulfoximines from sulfoxides.
Upon treatment of racemic sulfoxides with PhINTs (1.1 eq.) and copper(I) triflate (5 mol%) in dry toluene at room temperature for 12 hours, the corresponding sulfoximines were obtained with high yields (79-93%) (Scheme 19).



Scheme 19

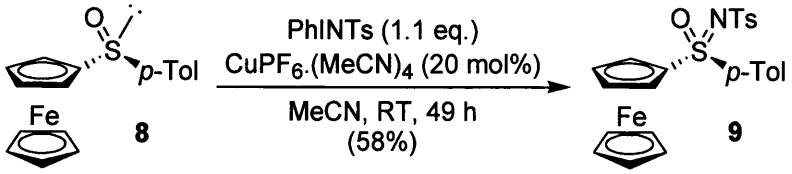
Sulfoxides **9** and **10**, containing C=C double bond reacted exclusively at the sulfur atom to give respectively sulfoximines **11** and **12** in good yields (Scheme 20).



Scheme 20

Other *N*-substituted iodine(III) species were synthesised, among them PhINNs[31] and PhINSes[39]. The latter was first used in copper-catalysed aziridinations of olefins leading to synthetically versatile Ses-protected aziridines. PhINSes was used later in sulfoximination reactions by Tye[40] in a comparative study of sulfoximination methods.

In 1999, Bolm investigated the synthesis of ferrocenyl sulfoximines and successfully obtained *N*-Ts and *N*-Ns sulfoximines.[31,41] In the standard conditions - PhINTs (1.1 eq.), $CuOTf.(C_6H_6)_{0.5}$ (5 mol%), dry toluene, 12 h - product **9** was obtained in very low yield; even after 50 hours of reaction, the yield did not exceed 8%. By changing the copper salt to a copper(I)-acetonitrile complex (20 mol%), sulfoximine **9** was synthesised in 58% yield from ferrocenyl sulfoxide **8** (Scheme 21).

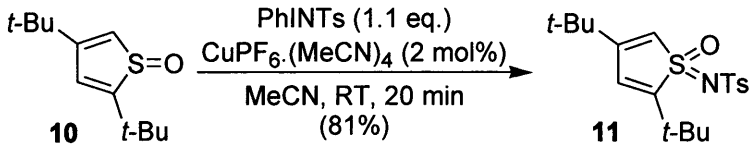


Scheme 21

When *N*-nosyliminophenyliodinane (PhINNs) was used as a nitrene donor, yields of the imination reaction of ferrocenyl sulfoxides increased notably (62-74%).

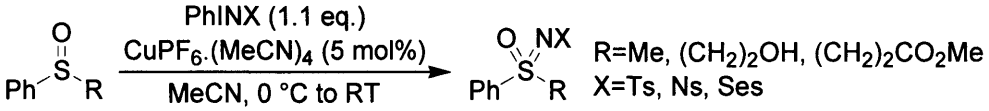
Such a difference of behaviour between *N*-tosyl- and *N*-nosyl- iminoiodinane had previously been observed by Andersson[42] in copper-catalysed aziridinations of alkenes.

Using the same methodology, Nakayama[43] reported the imination of thiophene sulfoxide **10**; with an even smaller amount of catalyst (2 mol%) and shorter reaction time, thiophene sulfoximine **11** was obtained in 81% yield (Scheme 22).



Scheme 22

In a comparative study of functional group compatibility of sulfoximination methods,[40] Tye reported the synthesis of several sulfoximines, using the same method described by Muller, in average to good yields (30-93%) (Scheme 23, Table 7).

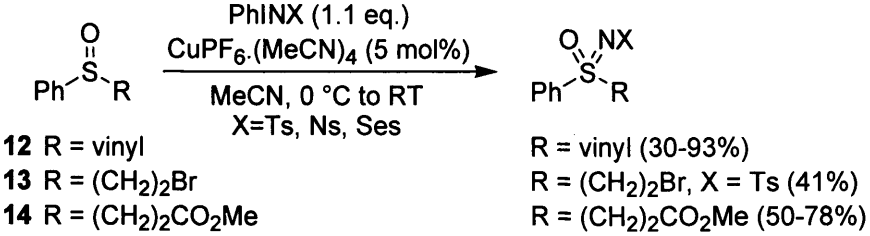


Scheme 23

Table 7: Yields of the imination reaction of sulfoxides.

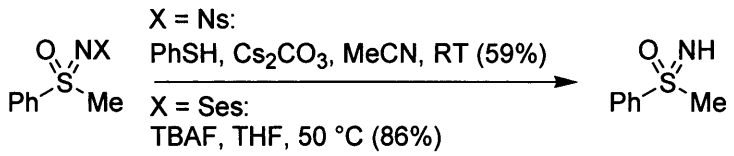
	PhI=NTs	PhI=NNs	PhI=NSes
R=Me	59	69	68
R=$(CH_2)_2OH$	90	40	59
R=$(CH_2)_2CO_2Me$	78	55	50

Imination with copper(I)-acetonitrile complex gave access to sulfoximines which were previously unavailable with the MSH procedure (Scheme 24). Sulfoxides **12** and **13** failed to react with MSH while sulfoxide **14** gave the corresponding *NH*-sulfoximine in only 4% yield.



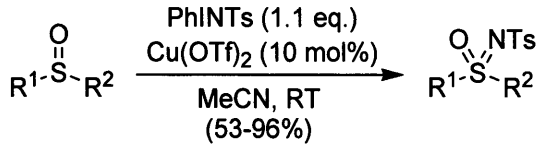
Scheme 24

Tye also described efficient deprotection methods for *N*-Ns and *N*-Ses protected sulfoximines, since *N*-Ts sulfoximines were generally difficult to turn into their *NH* counterpart, this possibility expanded the synthetic utility of *N*-sulfonyl derivatives (Scheme 25).



Scheme 25

In 2002, Malacria *et al.* reported that copper(II) triflate was highly efficient in this type of imination (Scheme 26).[44] Reaction of PhINTs (1.1 eq.) with sulfoxides in the presence of copper(II) triflate (10 mol%) in acetonitrile at room temperature, affords *N*-tosylsulfoximines in average to excellent yields (53-96%).



Scheme 26

Rather complex sulfoxides, either with hindered groups or triple bonds, were successfully converted into the corresponding sulfoximines (Figure 10).

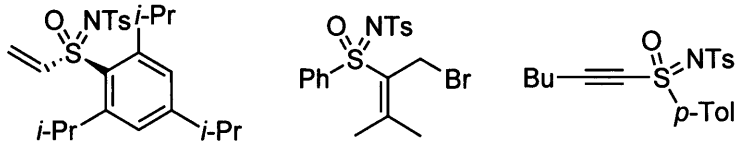
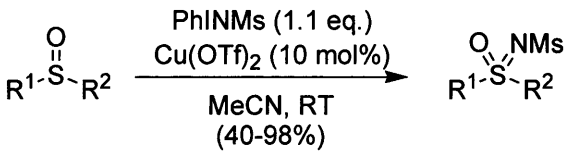


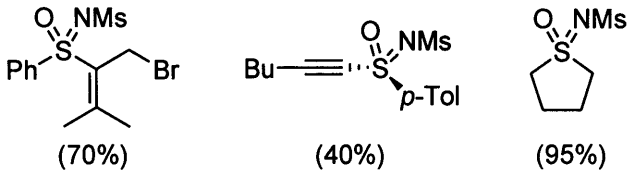
Figure 10

In order to see if the reaction was limited to arylsulfonyl iodinane species, the authors tested the imination reaction under copper(II)-catalysis with *N*-[(methylsulfonyl)imino]phenyliodinane PhINMs (Scheme 27).



Scheme 27

Using the same reaction conditions, they obtained a large variety of sulfoximines, thus demonstrating that the reaction was not limited to *N*-arylsulfonyl derivatives (Figure 11).



(70%) (40%) (95%)

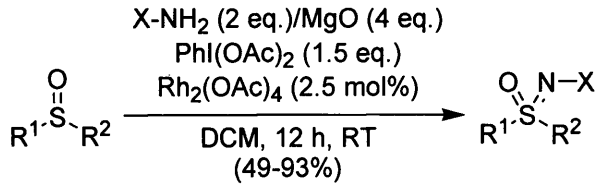
Figure 11

In conclusion, the discovery of copper-catalysed (and to a lesser extent iron-promoted) iminations has broadened the range of sulfoxides that can be converted to the corresponding sulfoximines; aryl-, alkyl-, vinyl- substituted sulfoxides and those with functionalised side-chains can be transformed into sulfoximines. *N*-Boc substituted sulfoximines are accessible with iron-mediation and the use of copper catalysts in combination with hypervalent iodine(III) species, allows the synthesis of different *N*-substituted sulfoximines (*N*-Ses or *N*-Ns) that were not accessible with classical methods. However, all copper catalysis protocols discussed so far are limited by the synthesis of the iminoiodinane species, and despite the various types of iminoiodinane listed previously and described in the literature[42, 45], their synthesis is not general. And in the case of iron catalysis, there are safety issues since Boc azide is a potentially explosive and health hazardous nitrene source.

1.2.3.2. Rhodium- and silver-catalysed imination

In 2004, Bolm described a new imination reaction using rhodium diacetate dimer $Rh_2(OAc)_4$ as catalyst.[46] In contrast to copper-catalysed imination methods, as in Bolm's

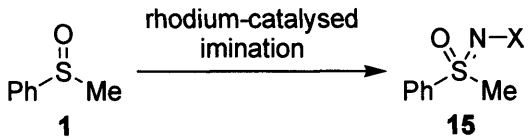
iron-mediated process (p22), the iminoiodinane is formed in situ by reaction of an amide or a sulfonamide with a hypervalent iodine reagent (Scheme 28).



Scheme 28

Rhodium-catalysed imination gave access to a large range of *N*-substituted sulfoximines in mild conditions. A mixture of amide or sulfonamide (2 eq.), MgO (4 eq.), PhIOAc (1.5 eq.) and rhodium catalyst (2.5 mol%) in DCM at room temperature, convert sulfoxides into sulfoximines in moderate to good yield (49-93%) (Table 8).

Table 8

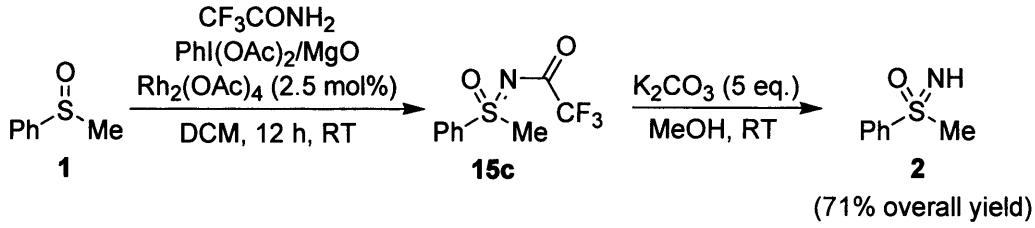


1 **15**

Entry	*X*	*Product*	*Yield (%)*
a	Ns	**15a**	86
b	Ms	**15b**	79
c	$CF_3C(O)$-	**15c**	84
d	Ac	**15d**	0
e	Bz	**15e**	0

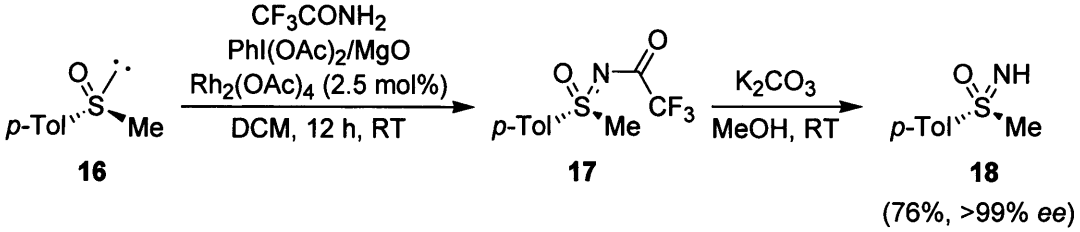
Using nosylamide (Entry a) under rhodium catalysis, sulfoximine **15a** was obtained in 86% yield; when PhINNs was synthesised before being used under rhodium catalysis, the same sulfoximine **15a** was obtained in 93% yield. Attempts to use acetamide (Entry d) and benzamide (Entry e) as nitrogen sources failed, suggesting that the intermediate iminoiodinanes should be stabilised by strong electron-withdrawing groups.

The most attractive result obtained with this system is the formation of *N*-trifluoroacetyl-protected sulfoximines such as **15c** in high yield (Entry c). Deprotection of these compounds by cleavage of the trifluoroacetyl group with potassium carbonate in methanol afforded the corresponding *NH*-sulfoximines in high yields. This two-step sequence does not even need isolation of the trifluoroacetyl-protected intermediate and leads to the synthetically valuable *NH*-sulfoximine **2** in good yields (66-88%) (Scheme 29).



Scheme 29

The stereospecificity of this reaction was examined using optically active methyl tolyl sulfoxide **16** (Scheme 30).

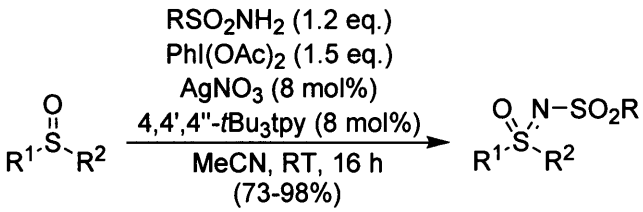


Scheme 30

Rhodium-catalysed imination followed by methanolysis of the protected intermediate **17**, afforded enantiopure sulfoximine **18** in good yield (76% overall yield, >99% ee). Examination of the sign of the optical rotation revealed that the reaction had proceeded with retention of configuration.

Rhodium catalysis presents real improvements in terms of flexibility and safety but the high cost of rhodium diacetate dimer is a major inconvenience and has motivated the quest for other catalytic or non-catalytic methods.

Around the same time, Bolm described a new protocol using a silver salt;[47] in this case, the use of silver salt was cheaper, reducing significantly the cost of the imination procedure. As previously observed for silver-catalysed aziridinations and intramolecular amidation,[48, 49] the imination reaction required a carefully selected combination of reagents. Several ligands, such as phosphines or diamines, were unsuccessful in catalysing the reaction, however terpyridine-based ligands used with silver nitrate afforded sulfoximines in good yields (73-98%) (Scheme 31).



Scheme 31

In the same way that the rhodium-catalysed reaction tolerated a large range of sulfonylamides, silver-catalysed imination is flexible; tosylamide or $SesNH_2$ for instance could react, but all attempts to use trifluoroacetamide as a nitrogen-donor species have failed under these conditions.

As for the scope of substrates that were suitable for this imination process, various sulfoximines were obtained in very good yields (Figure 12).

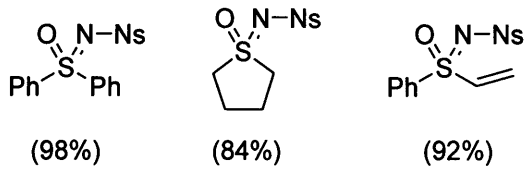
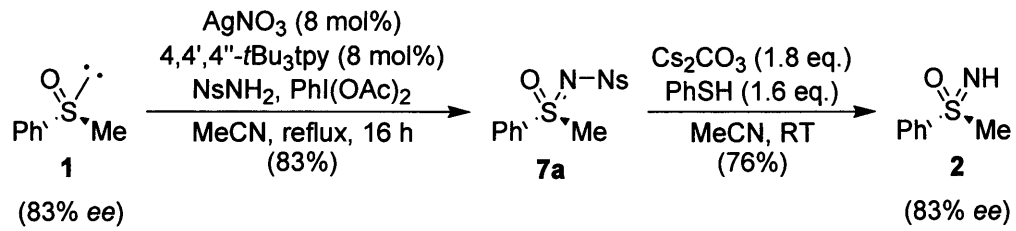


Figure 12

Silver-catalysed imination of optically active *(S)*-methyl phenyl sulfoxide **1** (83% *ee*), followed by deprotection of the resulting *N*-nosylsulfoximine **7a** by nucleophilic aromatic substitution with thiophenolate, gave the *NH*-sulfoximine **2** in 76% yield and 83% *ee*. The overall sequence proceeds with complete retention of configuration at the sulfur atom (Scheme 32).

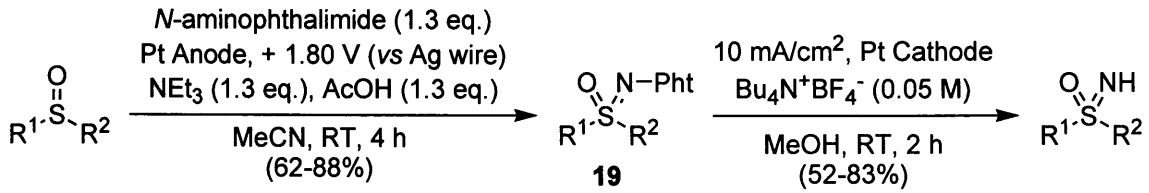


Scheme 32

In conclusion, the first real improvement of sulfoximination methods started with the use of copper salts. This catalytic system was particularly efficient for the synthesis of *N*-sulfonyl sulfoximines but the tosyl group is rather difficult to remove. Then, under rhodium catalysis several *N*-substituted sulfoximines were synthesised, such as trifluoroacetamide derivatives for which the easy deprotection leads to valuable *NH*-sulfoximines. Again the high cost of the rhodium catalyst led to research into other catalytic systems. The use of silver salts overcame the problem of the cost of the catalyst, unfortunately specific ligands were necessary to perform the conversion of the sulfoxide as silver salts alone failed to react.

1.2.4. Other recent methods

Nowadays, to have processes available for large scale synthesis, it is desirable to develop new methodologies avoiding the use of toxic or potentially unstable reagents as well as cheap protocols. In a 2002 report, Yudin investigated the application of their electrochemical nitrogen transfer methodology[50] to the imination of sulfoxides with *N*-aminophthalimide and subsequent deprotection to generate *NH*-sulfoximines (Scheme 33).[51]

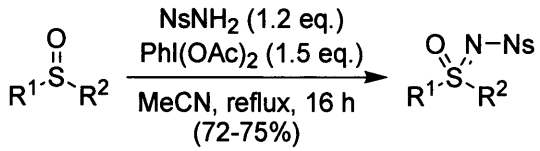


Scheme 33

In the case of phenyl vinyl sulfoxide **12**, no aziridination reaction occurred and sulfoximine **19a** (R^1=Ph, R^2=vinyl) was obtained in 70% yield. Enantiomerically enriched sulfoxide **16** (R^1=*p*-Tol, R^2=Me), 93% *ee* of the (*R*)-enantiomer, was subjected to the imination and the product **19b** analysed by HPLC, to reveal the same *ee* value. X-Ray analysis showed complete retention of configuration, *i.e.* imination proceeds without racemisation. Electrochemical N-N bond cleavage afforded the corresponding *NH*-sulfoximines in good yields (52-83%).

This study illustrates the use of the phenomenon called *overpotential*, which is the kinetic inhibition of electron transfer on a particular electrode surface. It allows a differentiation of substrates with similar redox potentials, which can be either reduced or oxidised at the electrode, based on their behaviour at the electrode/surface interface. This method avoids the use of oxidants and metal additives in redox reactions as well as metal catalysts in traditional organic reactions, and to date could be scaled up to 1 g based on the *N*-aminophthalimide.[52, 53]

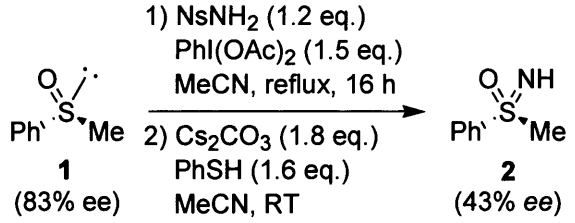
In related work, Bolm and his group investigated another imination process that did not involve metal catalysis (Scheme 34).[54]



Scheme 34

During the investigation of the scope of sulfonamides that could react, only nosylamide gave satisfactory results, no conversion or very low yields were observed with other nitrene-donor sources such as tosylamide or $SesNH_2$. No reaction was observed when this metal-free imination was carried out at room temperature, addition of a base (such as magnesium oxide) did not improve the reaction and neither did changing the solvent to DCM or THF.

When enantiomerically enriched *(S)*-methyl phenyl sulfoxide **1** (83% *ee*) was used in a two-step imination-deprotection process, partial racemisation was observed and *NH*-sulfoximine **2** was obtained with 43% *ee* only (Scheme 35).



Scheme 35

Since deprotection by nucleophilic aromatic substitution with thiophenolate anion, generated in situ from cesium carbonate and thiophenol, is known to proceed with retention of configuration, they attributed this loss to the high temperature and a long reaction time.

1.2.5. Synthesis of sulfoximines from sulfoxides: conclusion

Classical methods for imination reactions of sulfoxides are very often toxic and potentially explosive, or unsuitable for asymmetric transformations; deprotection of *N*-tosylsulfoximines to access the corresponding *NH*-sulfoximines is problematic due to drastic reaction conditions. The development of metal-promoted imination reactions is a real improvement regarding the various sulfoximines that can be synthesised by such transformations. These methods are also safer to carry out than the classic ones even though sulfoximination with hydrazoic acid is still an important industrial reaction.

The discovery of iron-promoted and mainly copper-catalysed iminations has broadened the range of sulfoxides susceptible to be converted to the corresponding sulfoximines; *N*-aryl, *N*-vinyl sulfoximines for example or those with functionalised groups attached to the sulfur can be now synthesised. *N*-Boc sulfoximines, accessible by iron-mediated imination, *N*-Ses or *N*-Ns substituted sulfoximines, synthesised by copper-catalysis in combination with hypervalent iodine(III) species or rhodium catalysis, were not accessible with classical

methods. The syntheses of new *N*-substituted sulfoximines represent a major improvement of the sulfoximine chemistry since they can be either deprotected smoothly to obtain the *NH* counterpart, or further functionalised.

Under rhodium catalysis several *N*-substituted sulfoximines were synthesised, such as very convenient trifluoroacetamide derivatives for which the easy deprotection leads to valuable *NH*-sulfoximines. Silver-catalysed imination is also a very flexible method and has the advantage of using a cheap catalyst, especially compared to rhodium-based methods. The electrochemical method is promising since no metal or oxidant is necessary and the "metal-free" sulfoximination protocol, of course, does not require a catalyst.

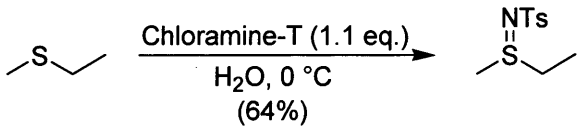
However, all these imination protocols have drawbacks. Iron-promoted imination with Boc azide, health hazardous and potentially explosive nitrene source give rise to safety issues, and in the case of copper catalysis, the procedures are limited by the synthesis of the iminoiodinane species. Rhodium catalysis presents real improvements in terms of flexibility towards the scope of substrates but the high cost of rhodium diacetate dimer is a major inconvenience. The use of silver salts is financially interesting but this method needs carefully determined reaction conditions and specific ligands to perform the conversion of the sulfoxide, as silver salts alone failed to react. As for the non-catalytic methods, the disadvantage of the electrochemical imination procedure is that this method can not be scaled up to large scale or industrial synthesis and the metal-free imination developed by Bolm gives partial racemisation as well as being restricted to the synthesis of *N*-Ns substituted sulfoximines.

1.2.6. Synthesis and oxidation of sulfilimines

1.2.6.1. Synthesis of sulfilimines

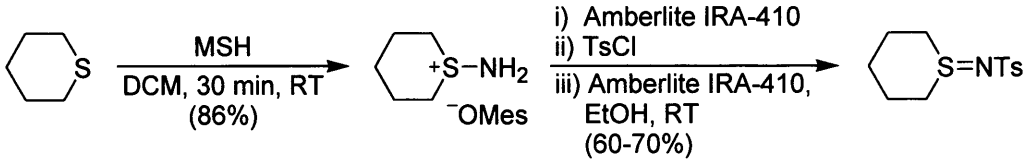
Sulfilimines were first reported in 1917[55] and some methods for their synthesis were already described, as well as some of their properties, in the early 1920's. The first studies reported the synthesis of sulfilimines in 1922 by reaction of the corresponding sulfides

with Chloramine-T[56, 57] (Scheme 36) or condensation of the corresponding sulfoxides with tosylamide in the presence of acetic anhydride or phosphorus pentoxide[58].



Scheme 36

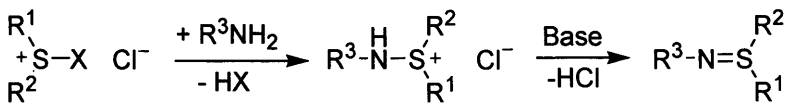
One of the first reports on the synthesis of sulfilimines involving other reagents than Chloramine-T or tosylamide, was published by Tamura *et al.* and described the reaction of MSH on sulfides (Scheme 37).[26]



Scheme 37

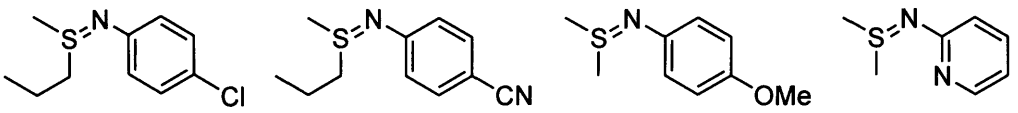
Sulfides and sulfoxides were successfully converted respectively, to sulfilimines and sulfoximines in good yields; sulfilimines were obtained in 72-90% yields and sulfoximines in 64-100% yields. Yields for the conversion of sulfilimines to the corresponding *N*-tosyl sulfilimines with the method described above were between 60 and 70%. Tamura also developed methods to synthesise different *O*-substituted hydroxylamines and described their reactivity towards several substrates including sulfides and sulfoxides.[59]

In 1975, Claus and co-workers presented the synthesis of *N*-aryl sulfilimines from sulfides.[60] The protocol consisted in converting sulfides into sulfonium salts with a good leaving group attached, and treating them with arylamines (Scheme 38).



Scheme 38

They described three methods in which the leaving group attached to the S-atom was different, (A) sulfide-NCS method (X=*N*-succinimidyl), (B) sulfide-*t*-BuOCl (X=O*t*-Bu) and (C) sulfide-SO_2Cl_2 (X=SO_2Cl), and obtained several sulfilimines in rather good yields (Figure 13). Yields indicated for the first three compounds are for the corresponding picrates since these sulfilimines were not stable at ambient temperature.



87% (A)
90% (B)

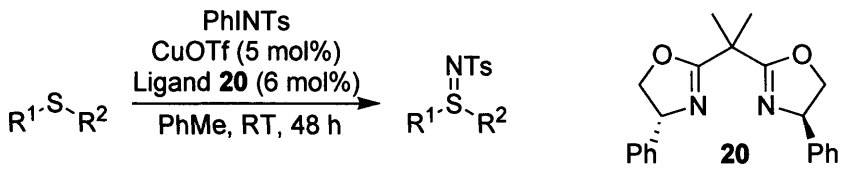
65% (A)

88% (A)
75% (C)

63% (A)

Figure 13

About twenty years later, the synthesis of chiral sulfilimines by treatment of prochiral sulfides with iminoiodinane PhINTs in the presence of copper(I) complexes was reported by Uemura *et al.*[37] As already stated in the introduction, the synthesis of sulfilimines can be considered in parallel to the synthesis of sulfoximines, since methods to access one or the other are generally quite similar. The synthesis of chiral sulfilimines has long been limited to the following two procedures; the conversion of the enantiomerically pure sulfoxides into the corresponding sulfimides by Cram *et al.*[61] and the kinetic resolution of racemic sulfilimines by Annunziata *et al.*[62] Inspired by independent studies on the aziridination of alkenes through hypervalent iodinane species,[35, 36] Uemura started to explore the possibility to synthesise chiral sulfilimines by application of this methodology (Scheme 39); chiral sulfilimines were obtained in moderate to high yields with up to 71% *ee* (Figure 14).



Scheme 39

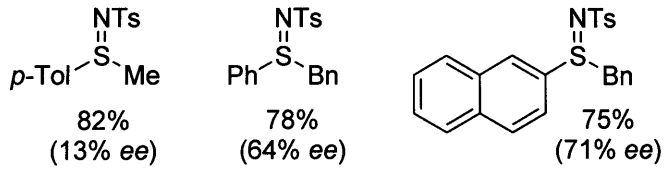
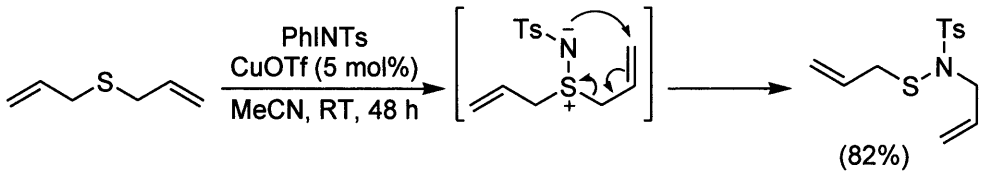


Figure 14

A year later, Uemura and Taylor investigated thoroughly the imination process by comparing reaction conditions for racemic and asymmetric syntheses of sulfilimines. The product (-)-methyl *p*-tolyl sulfimide has previously been assigned to be the *S* enantiomer,[61, 63, 64] since the sulfilimine produced by this imination method has a (+) optical rotation, the absolute configuration must be *R*. The absolute configuration of other sulfimides is not yet known, as the authors failed to obtain crystals suitable for X-Ray analysis, but may well be *R* by analogy with (-)-methyl *p*-tolyl sulfimide.

They also applied this reaction to allylic sulfides, the products were the corresponding sulfonamides (44-82% yields), produced via a [2,3] sigmatropic rearrangement of the initially formed allylic sulfilimines (Scheme 40).[65]



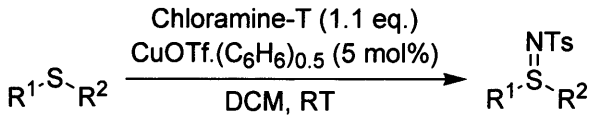
Scheme 40

However, as reported by Taylor in 1997,[66] a significant drawback of this method, apart from the low *ees* in the imidation reaction, is that it requires the synthesis of the nitrene donor or iminoiodinane species. They investigated then the reactivity of Chloramine-T to determine if it could be used as a nitrene transfer reagent in metal-catalysed imination reactions.

The reaction of Chloramine-T with sulfides to produce racemic sulfilimines is widely believed to proceed *via* an ionic mechanism. A side reaction of this imination procedure is the formation of the corresponding sulfoxides, due to the interception of the sulfonium intermediate by the water of crystallisation of Chloramine-T. In the case of a nitrene donor

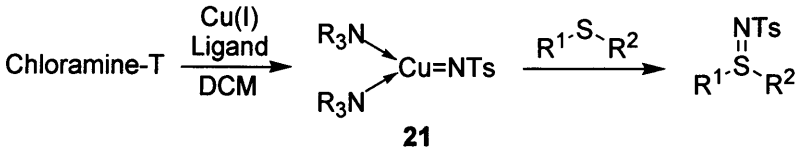
transfer mechanism, no intermediate is formed and thus no sulfoxide by-products are formed.

When the authors used Chloramine-T in place of phenyliodinane in copper-catalysed imination of sulfides (Scheme 41), they obtained similar results except for a significant reduction of the *ees* and the formation of sulfoxide by-products. Under these reaction conditions, although copper(I) catalyses the reaction of Chloramine-T with sulfides, the authors suggested that the reaction proceeds by an ionic mechanism with copper(I) acting as a Lewis acid.



Scheme 41

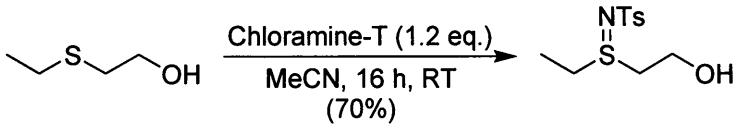
The same reaction in acetonitrile was exempt of sulfoxides and in DCM, when ligands (pyridine, bipyridine or triethylamine) were added, no sulfoxide formation was detected. They concluded that in the presence of a second ligand, the reactive intermediate **21** proposed by Jacobsen[67] can be formed and the nitrene transfer mechanism takes over (Scheme 42).



21

Scheme 42

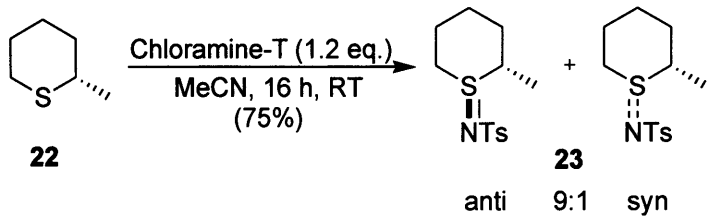
However, following observations reported in this work, Sharpless and Marzinzik found out that the use of a catalytic amount of copper triflate was highly detrimental to the yield of imination reactions.[68] With a slight excess of Chloramine-T (1.2 eq.) in pure acetonitrile, sulfilimines were successfully synthesised in 70-99% yields (Scheme 43). In regard of the procedure only, there are no real changes between the protocol from 1922 and the one described here, only the scope of substrates has expanded due partly to the fact that more substrates are soluble in acetonitrile than in water.



Scheme 43

The reaction between Chloramine-T and methyl *p*-tolyl sulfide was set up in the same conditions but water was intentionally added to the mixture, in 5, 10 and 15% volume; no sulfoxide formation was observed in any case.

Furthermore, in a study published in 1986 on the diastereoselectivity of sulfilimine formation[69] from sulfide **22** and Chloramine-T in methanol (the "traditional procedure"), the authors observed *anti*-**23** and *syn*-**23** in a 9:1 ratio, whereas when *t*-BuOCl and $TsNH^-$ were used, *syn*-**23** was noted as the major isomer. In the conditions of the "new procedure", sulfilimines were obtained in 75% yield and in a 9:1 *anti*:*syn* ratio, moreover, no sulfoxides by-products were observed (Scheme 44).

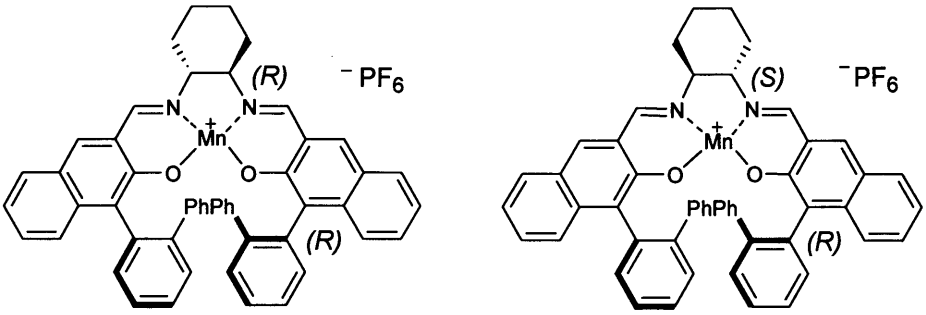


Scheme 44

The absence of sulfoxides and the observed anti preference are both consistent with the direct transfer of a TsN fragment to the less-hindered face of the sulfide in a rate-determining step. Presumably, Chloramine-T is a nitrene donor reagent that proceeds by nitrene transfer mechanism.

The enantioselective imidation of sulfides was also achieved by the Katsuki group in 1999 when a manganese-catalysed nitrene transfer protocol was developed.[70] They first found that a chiral (salen)manganese(III) complex was an efficient catalyst for the enantioselective aziridination of styrenes[71] and that a slightly modified chiral

(salen)manganese(III) complex was an excellent catalyst for enantioselective sulfoxidation of alkyl aryl sulfides.[72]

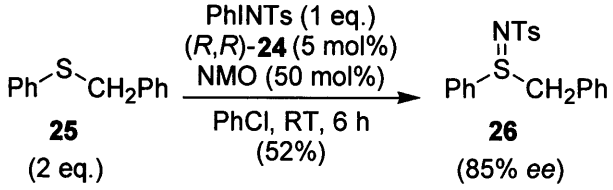


(*R*,*R*)-**24** (*R*,*S*)-**24**

Figure 15

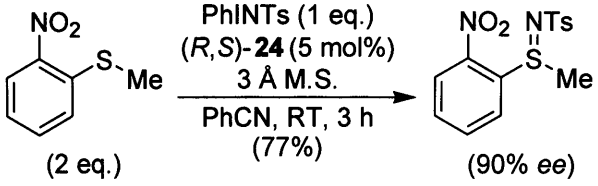
These two facts strongly suggested that such complexes (Figure 15), referred hereafter to as Mn(salen) complexes, could catalyse imidation of sulfides in an enantioselective manner. Although the mechanism of enantiotopic selection by Mn(salen) species was unclear, the authors believed it to be related to the conformation of the imino-Mn(salen) complexes. The conformation of a Mn(salen) complex is mainly dictated by i) the chirality of the five-membered chelate ring including Mn ion and ethylenediamine bridge, and ii) the nature of the apical ligand. In the case of an imino-Mn(salen) complex, the substituent attached to the nitrogen of the imino group also modifies the conformation and thus the enantioselectivity of the reaction.

Under optimised reaction conditions - Mn(salen) complex (*R*,*R*)-**24** (5 mol%) and apical ligand NMO (50 mol%) - imination of benzyl phenyl sulfide **25** using iminoiodinane PhINTs proceeded with high enantioselectivity (85% *ee*) and moderate yield (52%) (Scheme 45). Sulfinimidation was considered to proceed through an electrophilic Mn-imino intermediate.



Scheme 45

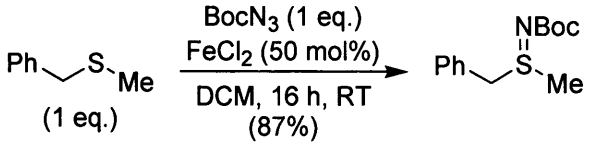
The authors then studied the influence of electron-withdrawing groups on the aromatic ring of the sulfide, expecting that the less nucleophilic substrate would give higher enantioselectivity than the parent phenyl methyl sulfide, which was used to optimise the reaction conditions described above. In this case (*R,S*)-**24** was a better catalyst than (*R,R*)-**24**, benzonitrile as solvent was superior to chlorobenzene, the use of a donor apical ligand was deleterious to both the yield and the enantioselectivity and finally, the addition of molecular sieves to the mixture increased the yield of the reaction (Scheme 46).



Scheme 46

However there is still room for improvement, especially in respect of enantioselectivity and the nitrene precursor. Azides are another nitrene donor species but except for tosyl azide, only a few of them have been used in imination reactions.

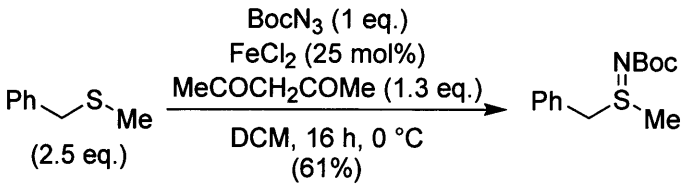
In 1998 Bach reported an iron-mediated imination of sulfoxides with Boc azide (cf § 1.2.3.1, p21).[29, 30] This process could be applied to the synthesis of sulfilimines and it was expected that the reaction with sulfides would be more efficient, due to the higher nucleophilicity of the sulfur atom in this class of compound. However, in the standard reaction conditions of nitrene transfer on sulfoxides, *i.e.* DCM, 0 °C, no reaction was observed. Upon warming to room temperature, reaction started and sulfilimines were synthesised in 27-92% yields (Scheme 47).



Scheme 47

S-Methyl-*S*-*tert*-butyl sulfilimine was obtained in 6% yield from the corresponding sulfide under the described reaction conditions; as in the sulfoxide case, the bulky substituent at the sulfur atom strongly inhibits the nitrene transfer.

Reaction at 0 °C required addition of a ligand that would solubilise the iron salt and thus accelerate the reaction. Acetylacetone was found to be the best suited for this purpose and yields of the imination reaction were moderate to good (36-90%) (Scheme 48).

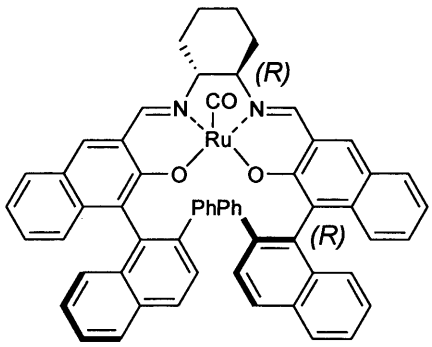


Scheme 48

As already stated while discussing this method for the synthesis of sulfoximines, the more significant aspect of this procedure is the formation of Boc protected sulfilimines, which can be easily converted into *NH*-sulfilimines.

The first asymmetric imination protocol using azides was developed by Katsuki *et al.* following another study on asymmetric aziridination. Jacobsen *et al.* reported that arylsulfonyl azides could be used as nitrene donors for asymmetric aziridination of olefins in the presence of copper(I) under photo-irradiation.[67] During their studies, Katsuki found that arylsulfonyl azides could serve as a nitrene precursors in the presence of (CO)Ru(II)(salen) complexes, hereafter referred to as Ru(salen) complexes, without photo-irradiation.[73] So a method for asymmetric sulfide imidation with arylsulfonyl azides in the presence of Ru(salen) complex was developed.[74]

The system was optimised using methyl phenyl sulfide as starting material, tosyl azide as nitrene donor and Ru(salen) complex (*R,R*)-**27** (Figure 16) as catalyst. When the equivalent Mn(salen) complex (*R,R*)-**24** was used (Figure 15), enantioselectivities were moderate.

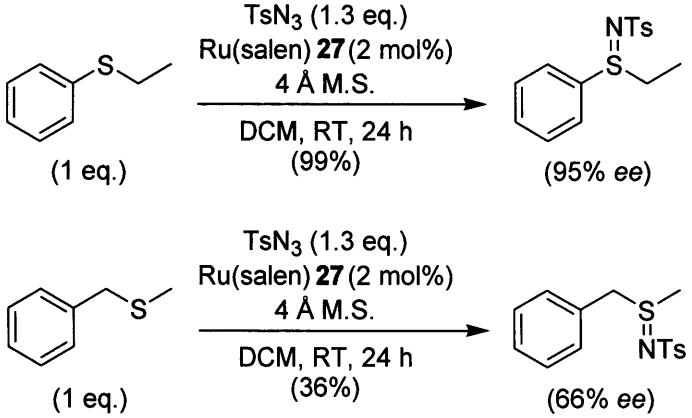


(*R*,*R*)-**27**

Figure 16

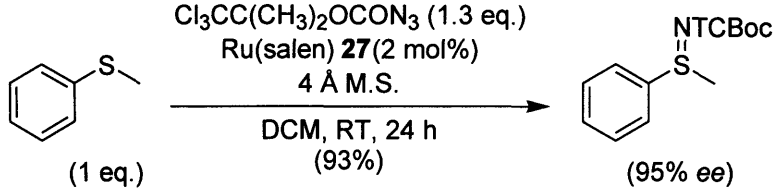
The authors then studied the reaction using different azides and observed that electronic effects of the substituents attached to the arylsulfonyl azide did not affect the enantioselectivity (>97% *ee*), but the yields were moderate (61-74%). Boc azide was also used but was found to be a poor precursor (22% yield, 71% *ee*).

The scope of substrates suitable for such transformation was then examined, using tosyl azide (1.3 eq.) and sulfide (1 eq.) in the presence of Ru(salen) (*R*,*R*)-**27** (2 mol%) and molecular sieves in DCM, at room temperature for 24 hours (Scheme 49). All the aryl methyl sulfides investigated were successfully converted to the corresponding sulfilimines (80-99% yields, 93-99% *ee*); with benzyl methyl sulfide, the yield and *ee* were markedly lower.



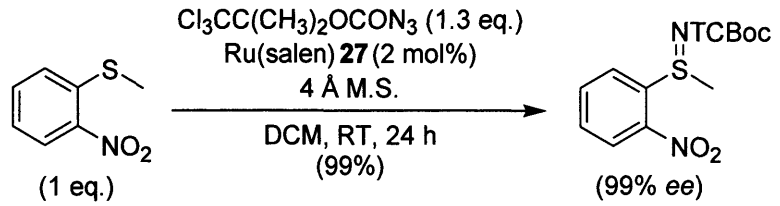
Scheme 49

The range of azide that could be used as nitrene donors was also investigated, especially *N*-alkoxycarbonyl azides.[75] It was with the very bulky TCBoc azide that the best yield and enantioselectivity were achieved in the imidation reaction of methyl phenyl sulfide (Scheme 50).



Scheme 50

With other nitrene donors such as acyl azides, benzoyl and *p*-nitrobenzoyl azides, alkyl azides, benzyl and *p*-nitrobenzyl azides, no desired reaction occurred.
The imidation of a range of alkyl aryl sulfides with TCBoc azide in the presence of catalyst Ru(salen) (*R,R*)-**27** under the same reaction conditions was then examined (Scheme 51).



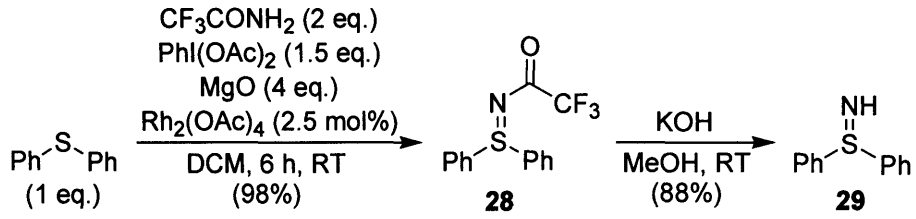
Scheme 51

The study was focused on the effect of *ortho* and *para* substitution on both the yield and the enantioselectivity of the imidation reaction. They concluded that introduction of electron-withdrawing or -donating groups in the *para* position did not affect either the yield or the *ee*, however, electron-withdrawing groups (bromo- or nitro-) in the *ortho* position increased the *ee* but did not affect the yield.

Regarding really recent improvements in the imination of sulfides or sulfoxides, Bolm and his group developed several methodologies simultaneously that have in common the use hypervalent iodine species and, in most cases, metal catalysts. In 2004, at the same time

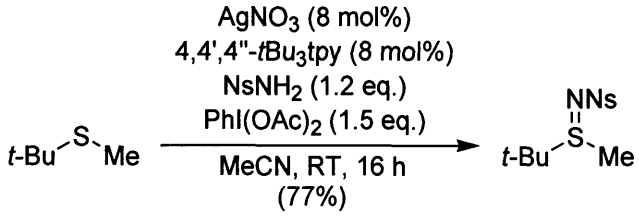
as Bolm developed his methodology to access unsubstituted *NH*-sulfoximines, experiments were carried out with sulfides to enhance the utility of this process.[46]

Under the same reaction conditions described previously (cf. § 1.2.3.2, p29) - *i.e.* sulfide (1 eq.), amide (2 eq.), $Rh_2(OAc)_4$ (2.5 mol%), $PhI(OAc)_2$ (1.5 eq.) and MgO (4 eq.) - sulfides were found to be more reactive than the corresponding sulfoxides. All reactions were completed within six hours and sulfilimines were obtained in most cases in high yield (61-98%). To demonstrate the applicability of this two-step protocol for the synthesis of *NH*-sulfilimines, intermediate **28** was deprotected using potassium hydroxide in methanol to lead to the corresponding "free" sulfilimine **29** in 88% yield (Scheme 52).



Scheme 52

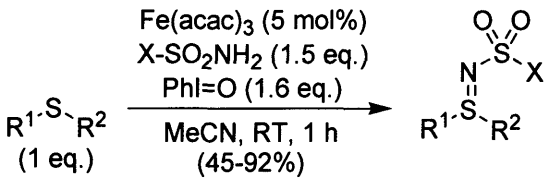
Again, when Bolm introduced a silver-catalysed method for the imination of sulfoxides, the same parallel was made with the sulfides.[47] The same procedure, under identical conditions, was applied to the conversion of sulfides to sulfilimines (Scheme 53).



Scheme 53

In contrast to the rhodium-catalysed imination, almost identical reactivities were observed in conversions of sulfides and sulfoxides to sulfilimines and sulfoximines respectively.

Bolm also developed an iron-catalysed imination of sulfoxides and applied this protocol to the imination of sulfides (Scheme 54).[32]



Scheme 54

Reaction of sulfide (1 eq.), sulfonamide (1.5 eq.) and iodosylbenzene (1.6 eq.) in the presence of iron(III) acetylacetonate, under the same conditions used for imination reaction on sulfoxides, afforded sulfilimines in moderate to high yields (45-92%). As observed with rhodium-catalysed imination, the more nucleophilic sulfides showed high reactivity and the reaction time decreased notably, from several hours (14-20 h) for the conversion of sulfoxides to 1 hour for sulfides.

This increased reactivity allowed imination of bulky sulfides (mesityl group) and the use of hindered sulfonylamides (*t*-butylsulfonylamide) that failed to react on the corresponding sulfoxides (Figure 17).

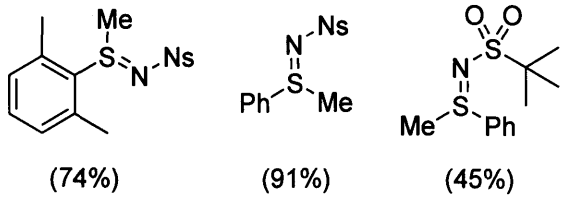
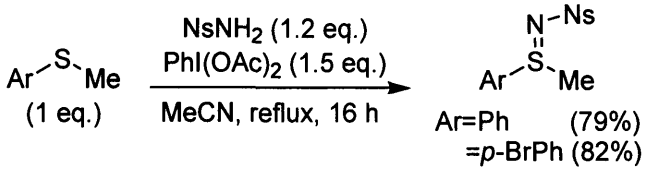


Figure 17

Finally, as a result of simultaneous application of imination reaction methodologies listed previously to both sulfoxides and sulfides, Bolm *et al.* developed a metal-free protocol for the imination of sulfides (Scheme 55).[54]



Scheme 55

1.2.6.2. Oxidation reactions of sulfilimines

In the late 1970s, a few methods for the oxidation of sulfilimines had been reported, including the use of potassium permanganate in neutral or basic solution,[15, 60, 76, 77] although yields were often poor and some sulfoximines could not be prepared by this method.[76, 78] Cyclic sulfilimines have been oxidised by sodium periodate[79] and one example of oxidation with *m*-CPBA was reported.[61]
However, the use of potassium permanganate was essentially the best protocol to synthesise sulfoximines from sulfilimines. For example, diarylsulfoximines were not available from imination of diarylsulfoxides, but oxidation of diarylsulfilimines with potassium permanganate led to the synthesis of diarylsulfoximines in very good yields (80-95%).[80]

In 1977, Swern developed an oxidation procedure using ruthenium tetroxide, generated *in situ* with a catalytic amount of ruthenium dioxide and cooxidant sodium periodate in a biphasic system.[81] This method was only tested on *S,S*-dimethylsulfoximines, but for several *N*-substituted sulfilimines, the corresponding sulfoximines were obtained in high yields (86-95%).

A year later Johnson reported the oxidation of *N*-tosylsulfilimines to *N*-tosylsulfoximines with alkaline hydrogen peroxide,[82] yields were low (29% for benzyl phenyl sulfoximine) to excellent (98% for methyl phenyl sulfoximine).

In 1979 Swern used *m*-chloroperoxybenzoate anion, generated by a mixture of *m*-CPBA and potassium carbonate in ethanol and water at room temperature, to oxidise sulfilimines to sulfoximines in good yields (69-97%).[83]

Oae *et al.* published in 1984 an oxidation method for *S,S*-diaryl-*N*-tosyl sulfilimines and *S*-aryl-*S*-alkyl-*N*-sulfonyl substituted sulfilimines based on sodium hypochlorite in a biphasic system.[84] The use of sodium hypochlorite (2 eq.) in EtOAc/DCM/H_2O in the presence of an ammonium salt (Bu_4NBr for example) converted sulfilimines into the corresponding sulfoximines in good yields (61-100%).

At the same time Ketcha reported the oxidation of *N*-tosylsulfilimines in the presence of peroxyacetic acid (2 eq.) and a catalytic amount of ruthenium dioxide (0.02 eq.) in a biphasic system DCM/H_2O, yielding sulfoximines in high yields (70-100%).[85]

Detailed discussion of all of these procedures is beyond the scope of this review.

1.2.6.3. Conclusion

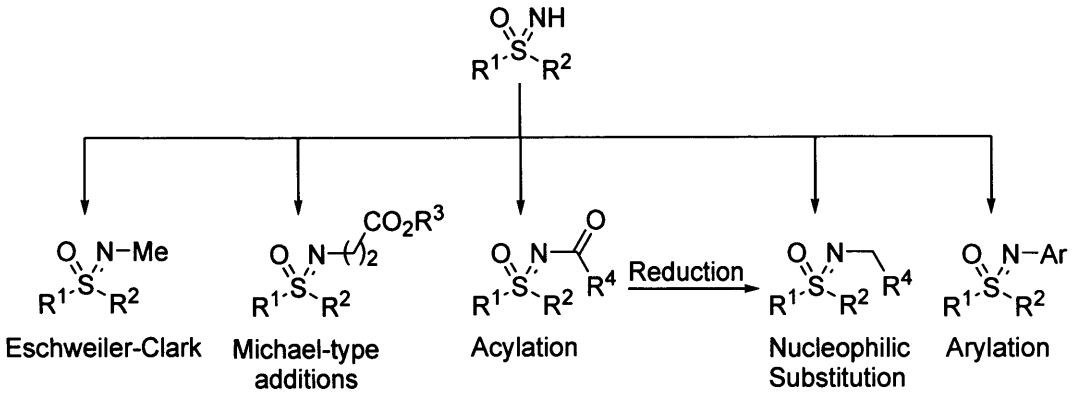
In the same manner the syntheses of sulfoximines from sulfoxides could be divided in two groups, syntheses of sulfilimines can be classified as following, the classical methods or metal-catalysed iminations after 1996. Classical methods were rather efficient but the scope of substrates suitable for such transformations was limited to simple alkyl and aryl sulfides. As for the substituent attached to the nitrogen, only tosyl derivatives (Chloramine-T, tosyl azide) or *NH*-sulfilimines (MSH) were accessible.

Since 1996, when copper-catalysed imination of sulfides was introduced, the range of nitrene precursors expanded; with hypervalent iodine(III)-based procedures various amides (trifluoroacetamide, *tert*-butylsulfonylamide, nosylamide) were successfully tested and several azides (Boc, TCBoc azides), in the presence of appropriate metal catalyst, yielded synthetically valuable sulfilimines.

Although sulfilimines are of interest in themselves, when included in the synthesis of sulfoximines they are difficult to exploit. These compounds are not as stable as sulfoxides and with the harsh oxidation conditions for their conversion to the corresponding sulfoximines, this route is far less developed. It is generally easier to synthesise sulfoximines from sulfoxides, as methods for oxidation of sulfides to sulfoxides are well established, than to follow the sulfide-sulfilimine-sulfoximine pathway.

1.2.7. Derivatisation of *NH*-sulfoximines

Derivatisation can usually be achieved by deprotonation of the acidic *N-H* proton, followed by addition of an appropriate electrophile to the weakly nucleophilic anion, to form either *N*-alkylated or *N*-acylated sulfoximines; with the exception of the synthesis of *N*-methyl sulfoximines which can be carried out under Eschweiler-Clark conditions (Scheme 56).



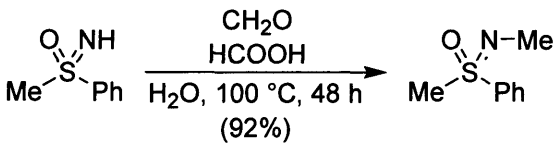
Scheme 56

In contrast, access to *N*-aryl sulfoximines is rather more difficult. Until recently, it could only be achieved either by oxidation of *N*-aryl sulfilimines or by conversion of *N*-aryl sulfonimidoyl halides by treatment with organometallic reagents.

Considering the obvious disadvantages of these processes - harsh reaction conditions, insufficient functional group tolerance and tedious preparation of sulfonimidoyl halides, toxicity and safety issues - to find new derivatisation methods is an on-going challenge in the chemistry of sulfoximines.

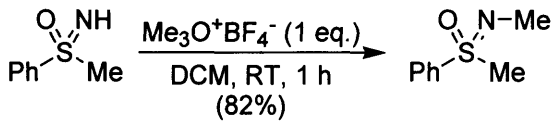
1.2.7.1. *N*-vinyl, *N*-acyl and *N*-alkyl sulfoximines

N-Methyl sulfoximines were among the first *N*-alkyl sulfoximines to be reported. Their synthesis can be carried out under Eschweiler-Clark conditions, that is the use of aqueous formaldehyde in formic acid at refluxing temperature (Scheme 57).[86]



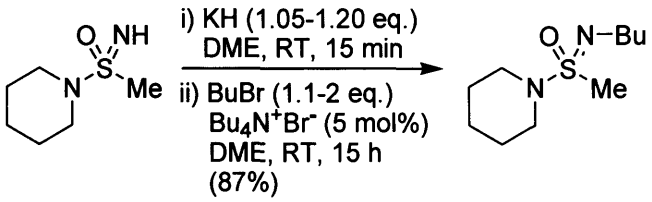
Scheme 57

N-Methyl and *N*-ethyl sulfoximines are also available from reaction of *NH*-sulfoximines with strongly electrophilic alkylating agents such as trialkyloxonium salts. (Scheme 58)[19]



Scheme 58

N-Alkyl sulfoximines can be synthesised by nucleophilic substitution after deprotonation of the rather acidic imino proton.[87] Johnson used this method to access *N*-alkyl-*N',N'*-dialkyl sulfonimidamides, a new class of sulfoximine analogues, from the corresponding *N*-hydrido-*N',N'*-dialkyl sulfonimidamides (Scheme 59).

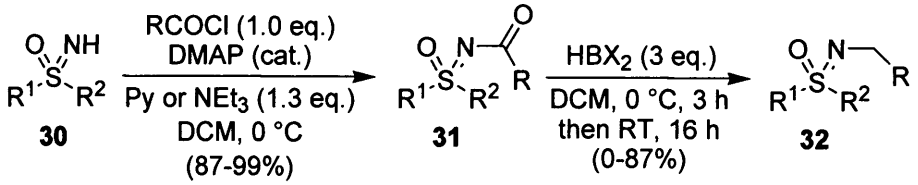


Scheme 59

Finally, there were not many ways to synthesise *N*-alkyl sulfoximines from the corresponding NH counterparts and until a mild synthetic procedure was developed, only restrictive methods - harsh conditions, limited scope of substrates - were available.

A major improvement was reported by Bolm and his group in 2002 when a two-step protocol for the formation of *N*-alkyl sulfoximines was established.[88] Acylation of *NH*-sulfoximine followed by reduction of the intermediate affords *N*-alkyl sulfoximines in high yields (up to 87%) (Scheme 60).

Based on the work by Brown who has demonstrated the use of boron reagents in the reduction of amides to amines,[89] Bolm first investigated the reduction of simple *N*-acylated sulfoximines with complexed boranes (Table 9).



30 **31** **32**

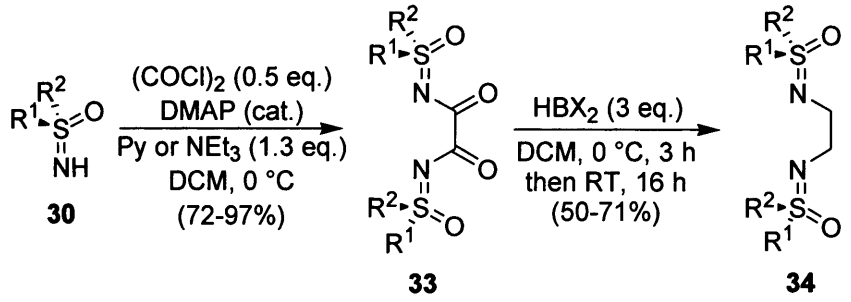
Scheme 60

Table 9

Entry	*R*	*Yield Acylation (%)*	*Reducing Agent HBX_2*	*Yield Reduction (%)*
a	Me	99	$BH_3.SMe_2$	70
b	*t*-Bu	98	$BH_3.SMe_2$	62
c	*n*-Heptyl	87	Catecholborane	87
d	2-BrC_6H_4	97	Catecholborane	0
e	4-ClC_6H_4	97	Catecholborane	0
f	4-ClC_6H_4	97	$BH_3.SMe_2$	12
g	4-ClC_6H_4	97	BH_3.THF	37

Acylated sulfoximines **31** prepared from **30** and aliphatic acyl chlorides could be reduced smoothly, furnishing the desired products **32** in good yields (Entries a-c). Particularly noteworthy is the synthesis of *N*-(*neo*-pentyl) sulfoximine (Entry b) since this compound cannot be obtained by standard S_N2 type substitution reactions. Surprisingly, benzoyl-containing substrates did not react at all or their reduction gave the corresponding products **32** in very low yields (Entries d-g). Neither changing the borane source nor modifying the reaction conditions, significantly improved the yield. For the synthesis of these substrates, the standard S_N2 type substitution reactions with benzyl halides[87] is still advantageous over this two-step process described by Bolm.

An interesting application of this protocol is the synthesis of ethylene-bridged C_2-symmetric bissulfoximines **34**, compounds that appear attractive due to their potential as ligands in metal catalysis and their analogy to salens (Scheme 61).[90, 91]



30 **33** **34**

Scheme 61

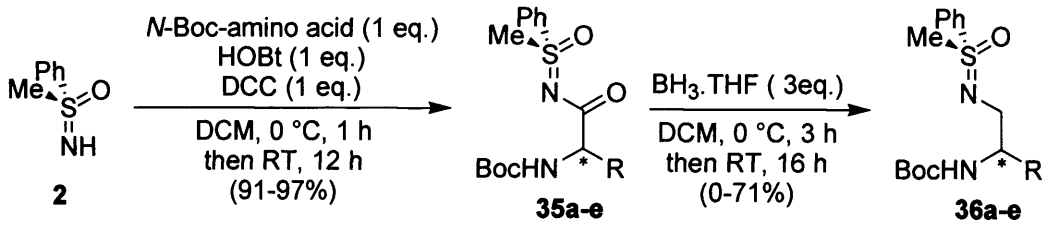
Table 10

Entry	*R^1*	*R^2*	*Reducing Agent HBX_2*	*Yield Acylation (%)*	*Yield Reduction (%)*
a	Me	Ph	BH_3.THF	80	68
b	*i*-Pr	Ph	BH_3.THF	88	66
c	4-PhC_6H_4	Me	catechol-borane	68	50
d	3,5-(*t*-Bu)-C_6H_3	Me	catechol-borane	72	66
e	Tol	2-MeO-C_6H_4	catechol-borane	97	71

This reaction sequence has been applied to a variety of alkyl- and aryl- substituted sulfoximines **30** (Table 10). Generally good yields were obtained for the acylation step, up to 97%, and reduction of the intermediate **33** afforded ethylene-bridged bissulfoximines **34** in average to good yields (50-71%).

Recently Bolm obtained new pseudopeptides with sulfoximines in the peptide chain,[92] their synthesis involved DCC/HOBt couplings between sulfoximines and *N*-protected α-amino acids. The authors wondered if such compounds **35** could be reduced using the same

methodology as applied to simple *N*-acyl sulfoximines (Scheme 62, Table 11). After optimisation of the protocol (Entry a), borane-THF complex was found to be a better reductant than catecholborane or borane-DMS complex, which gave very low yields or no conversion at all.



Scheme 62

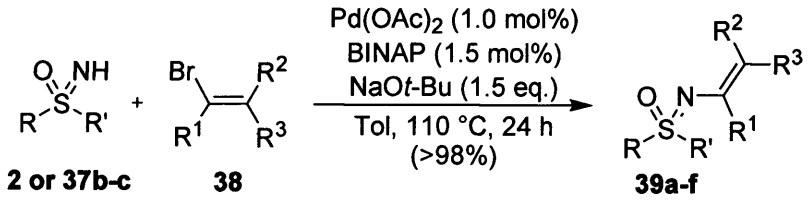
Table 11

Entry	*Configuration of* ***35***	*Amino Acid*	*R*	*Yield Acylation (%)*	*Yield reduction (%)*
a	(*S,S*)	(*S*)-Ala	Me	92	68
b	(*S,S*)	(*S*)-Leu	*i*-Bu	97	71
c	(*S,S*)	(*S*)-Val	*i*-Pr	96	66
d	(*S,R*)	(*R*)-Val	*i*-Pr	97	62
e	(*S,S/R*)	rac-Val	*i*-Pr	97	67

Leucine and valine derived compounds react equally well (Entries b, c) giving the corresponding β-amino sulfoximines **35b** and **35c** in 71% and 66% yield respectively. In order to ensure that the reduction step proceeded without epimerisation of the stereogenic centre at the α-position of the carbonyl, both diastereoisomers formed from (*S*)-**2** and (*S*)-valine, (*S*)-**2** and (*R*)-valine, were synthesised. These intermediates (*S,S*)-**35c** and (*S,R*)-**35d** were then reduced both separately (Entries c, d) and as a diastereomeric mixture (Entry e) and analysed by ^{1}H NMR spectroscopy, which showed the absence of undesired diastereoisomers and confirmed that no epimerisation had occurred during the carbonyl reduction.

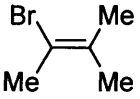
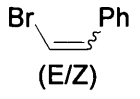
This reaction sequence with the initial DCC/HOBt mediated acylation represents an example of *N*-alkylation of sulfoximines under base-free conditions. Furthermore, these transformations are mild enough to fully retain the stereochemistry at the stereogenic carbon atom in the alkyl substituent.

Derived from continuous studies of sulfoximines and their potential in metal catalysis, Bolm *et al.* developed a palladium-catalysed cross-coupling protocol for the synthesis of *N*-vinyl sulfoximines,[93] a previously unavailable class of compounds (Scheme 63). Under these optimised conditions - palladium diacetate (1.0 mol%), BINAP (1.5 mol%) and sodium *tert*-butoxide (1.5 eq.) - the coupling proceeds with complete conversion within 24 hours. *N*-Vinyl sulfoximines **39** are water- and acid-sensitive, the reaction mixture is thus diluted with diethyl ether and filtered through a plug of celite, which keeps the work-up in dry and nonacidic conditions, giving essentially pure sulfoximine in excellent yields (>98%). Studies of the scope of substituted sulfoximines and vinyl bromides **38** suitable for this coupling show that this method is rather flexible (Table 12).



Scheme 63

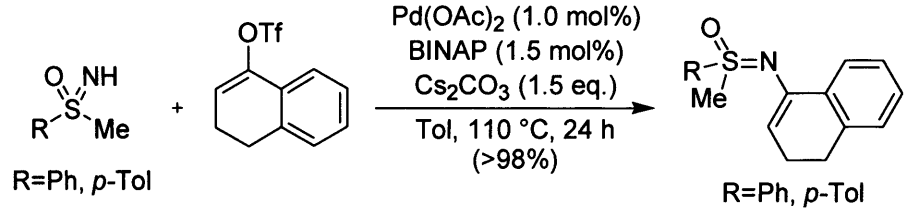
Table 12

Entry	***SM** : R/R'*	*Vinyl Bromide **38***	***39**: Yield (%)*
a	**2** : Me/Ph		>98
b	**37b** : Me/2-MeO-C_6H_4		>98
c	**37c** : -$(CH_2)_4$-		>98
d	**2** : Me/Ph		>98
e	**2** : Me/Ph		>98
f	**2** : Me/Ph	 (E/Z)	0

Alkyl, aryl *NH*-sulfoximines such as **2** and **37b** or cyclic one such as **37c**, can be converted in high yields to their *N*-vinyl counterparts **39a-c** (Entries a-c). Simple vinyl bromides can be coupled to *NH*-sulfoximines (Entry d) and even 2-bromo-3-methylbut-2-ene (Entry e), a sterically very demanding vinyl bromide, was a suitable substrate. β-Bromostyrene (Entry f) was also tested as coupling partner for methyl phenyl sulfoximine **2** but in contrast to the other results, no product could be isolated and neither starting material nor vinyl bromide could be recovered after work-up of the reaction. This fact

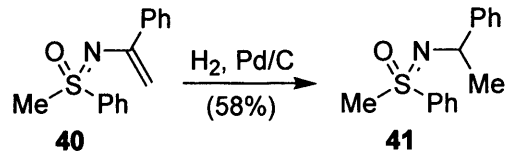
suggests that the instability of the coupled product, rather than a low reactivity of the substrates, is the reason for the failure of this experiment.

Quite recently, vinyl triflates were found to be suitable partners in palladium-catalysed couplings with amines[94] and amides[95]. With the goal to broaden the scope of substrates, the authors also investigated palladium coupling with such compounds. When a softer base such as cesium carbonate was used, couplings of sulfoximines with vinyl triflates were completed in 24 hours in almost quantitative yields (Scheme 64).



Scheme 64

Initial studies of the reactivity of *N*-vinyl sulfoximines were undertaken and for this purpose, reduction with sodium borohydride was chosen as a test reaction. Unfortunately all attempts to reduce the *N*-vinyl sulfoximine with sodium borohydride with different conditions failed and no expected product was isolated. However, hydrogenation of **40** with palladium over charcoal formed product **41** as a mixture of diastereoisomers (dr=4:1) in 58% yield (Scheme 65).[93]

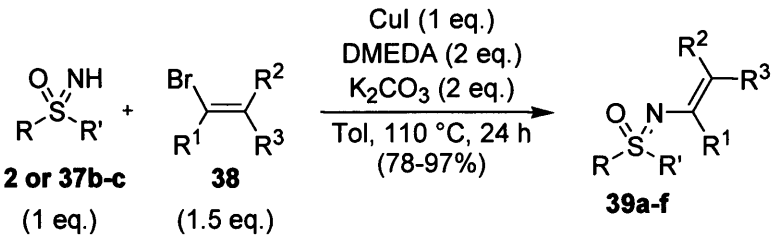


40 **41**

Scheme 65

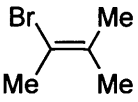
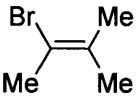
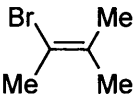
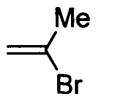
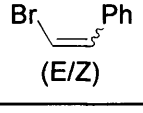
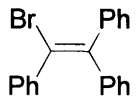
The palladium-catalysed coupling methodology is rather efficient but suffers from two major drawbacks; the cost of the palladium catalyst and BINAP ligand, and the limited range of vinyl bromides suitable for such coupling, motivated the search for a more general protocol. Bearing in mind these disadvantages, Bolm developed a copper-mediated coupling with vinyl bromides (Scheme 66).[96]

First attempts to perform this coupling in the presence of copper iodide (1 eq.) and potassium carbonate (1.5 eq.) did not lead to the expected product. Keeping in mind Buchwald's observation that 1,2-diamines were suitable ligands for copper-promoted C-N bond formation, Bolm and his group soon investigated the effect of such ligands on copper-mediated sulfoximine/vinyl bromide cross-coupling. Finally, using DMEDA (2 eq.) as ligand in the presence of copper iodide (1 eq.), potassium carbonate (2 eq.), vinyl bromide (1.5 eq.) and sulfoximine (1 eq.) in toluene at 110 °C for 24 h, several *N*-vinyl sulfoximines were obtained in good yields (78-97%) (Table 13).



Scheme 66

Table 13

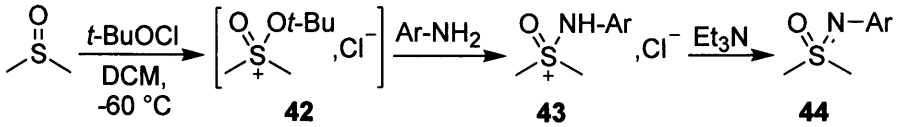
Entry	***SM** : R/R'*	*Vinyl bromide*	***39**: Yield (%)*
a	**2** : Me/Ph		94
b	**37b** : Me/2-MeO-C_6H_4		93
c	**37c** : -$(CH_2)_4$-		91
d	**2** : Me/Ph		97
e	**2** : Me/Ph		90
f	**2** : Me/Ph		78

As in the palladium-catalysed coupling, alkyl, aryl or cyclic NH-sulfoximines can react with rather simple vinyl bromides (Entries a-c) in very good yields (91-94%). Furthermore, in contrast to palladium-catalysed coupling, copper-promoted reaction of methyl phenyl sulfoximine **2** with β-bromostyrene (Entry e) was successful (90% yield) and proceeded with complete retention of configuration. Vinylation with 1,2,2-triphenylvinyl bromide (Entry f) formed the corresponding sulfoximine **39f** in 78% yield, this example illustrates well the broadening of the type of substrate suitable for this method.

1.2.7.2. *N*-Aryl sulfoximines

The development of new methodologies to create C-N bonds has been an area of great interest in the last ten years since the Buchwald[97] and Hartwig[98] groups independently reported in 1995 the first catalytic amination of aryl bromides with free amines. In this context, metal-promoted cross-coupling reactions of nitrogen nucleophile with appropriate electrophiles (halides or triflates), has emerged as a prolific research area. The synthesis of *N*-aryl sulfoximines is also of interest and several methods starting from *NH*-sulfoximines have been developed to replace rather inconvenient protocols in use until then.

For instance, *N*-aryl-*S,S*-dimethylsulfoximines could be obtained by complexation of DMSO with *tert*-butyl hypochlorite at low temperature, followed by reaction of the complex with arylamines to give *N*-aryl-*S,S*-dimethylazasulfoxonium chlorides, which upon treatment with base, yielded *N*-aryl-*S,S*-dimethylsulfoximines (25-70%) (Scheme 67).[99]

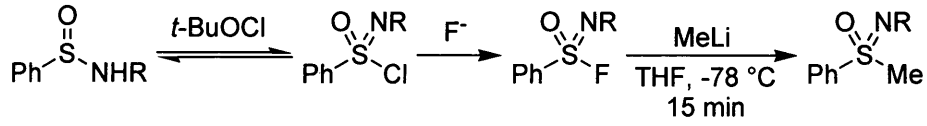


42 **43** **44**

Scheme 67

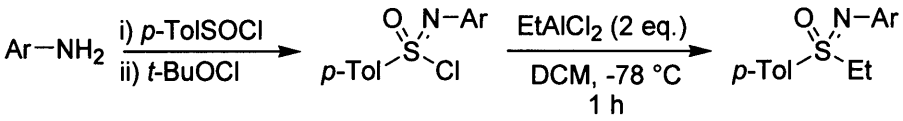
Reaction of sulfonimidoyl fluorides with primary alkyllithiums led to the formation of sulfoximines in average to good yields (27-89%).[100] This experiment was successful with alkyl as well as aryl sulfinamides. Reaction of sulfonimidoyl chlorides with alkyllithiums led

to the corresponding sulfinamides so their conversion into sulfonimidoyl fluorides was necessary to obtain sulfoximines (Scheme 68).



Scheme 68

Another procedure has been developed by Harmata[101] to access specifically *N*-aryl-*S*-ethyl sulfoximines (Scheme 69).

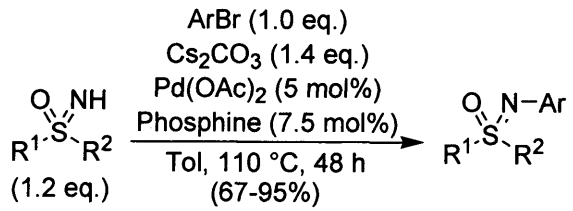


Scheme 69

N-Benzyl-, *N*-nosyl- and *N*-mesityl *S*-ethyl-*S*-tolylsulfoximines were synthesised in moderate yields (63, 76 and 41% yields respectively).

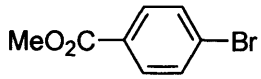
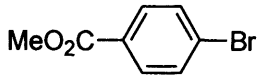
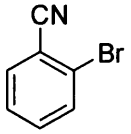
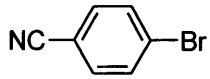
In the late 1990s, Buchwald's and Hartwig's palladium-catalysed amination process had become a general method to synthesise arylamines and had been extended to the synthesis of arylated imines and azoles. In 2000, Bolm applied this methodology to the synthesis of *N*-aryl sulfoximines.[102]

In the presence of aryl bromide (1.0 eq.), cesium carbonate (1.4 eq.) and a bidentate phosphine ligand (BINAP or TolBINAP) with palladium diacetate (Scheme 70), several *N*-aryl sulfoximines (1.2 eq.) were synthesised with 67-95% yield (Table 14).



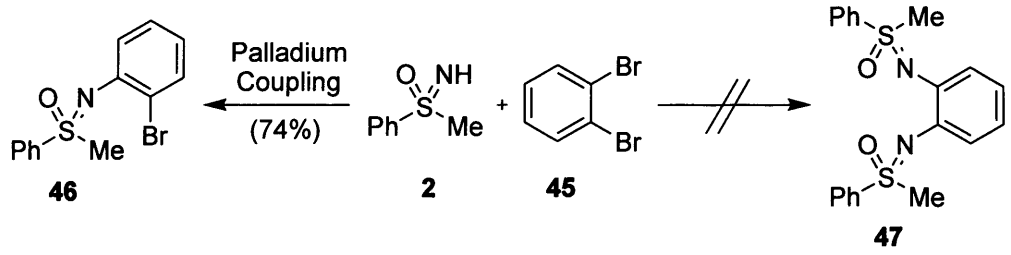
Scheme 70

Table 14

Entry	*R^1*	*R^2*	*Ar-Br*	*Yield (%) BINAP*	*Yield (%) TolBINAP*
a	Me	Me		94	90
b	Me	Me	Ph-Br	86	95
c	Me	Ph		89	90
d	Me	Ph		94	91
e	Me	Ph	Ph-Br	72	83
f	Me	*p*-Tol		88	93

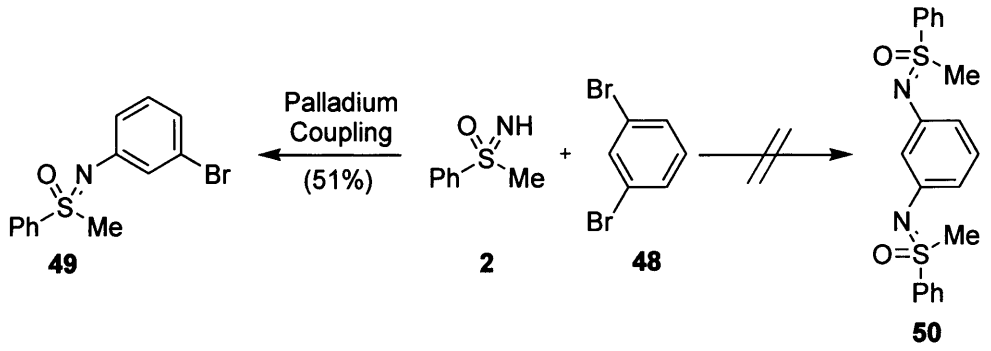
A comparison of the yields obtained with BINAP and TolBINAP shows that these ligands differ only slightly in their effectiveness. Reactions with aryl bromides bearing electron-withdrawing substituents proceeded smoothly (Entries a, c, d, f) and the yields of the corresponding *N*-aryl sulfoximines were uniformly high regardless of the substitution position of the arylbromide (Entries d, f) or the sulfoximine (Entries a-c, e).

Since the authors have been involved in the development of C_2-symmetric bissulfoximines as ligands in asymmetric catalysis (Type **C2**, Figure 19), they decided to try palladium-catalysed coupling of 1,2-dibromobenzene **45** (1.0 eq.) with methyl phenyl sulfoximine **2** (2.5 eq.) under the standard conditions (Scheme 71).



Scheme 71

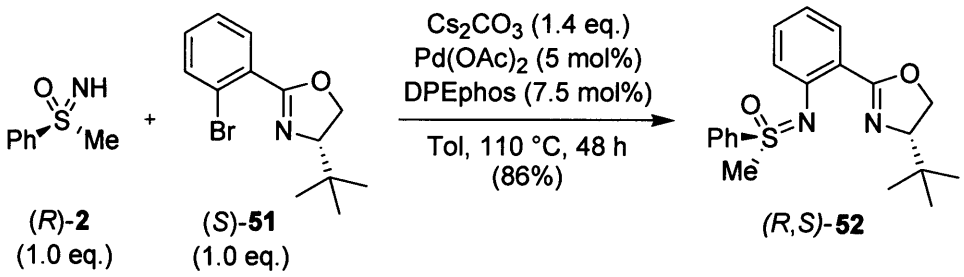
Only the monosulfoximidoyl product **46** was obtained albeit in respectable yield (74%) and neither changing the ligand nor the reaction conditions gave bis-imination product **47.** The same results were obtained when the palladium-catalysed coupling was carried out with 1,3-dibromobenzene **48**, only the monosulfoximine **49** was synthesised in 51% yield (Scheme 72).



Scheme 72

During studies of palladium-catalysed arylation of chiral amines led by Buchwald, partial racemisation was observed,[103] mainly due to β-elimination of the hydrogen atom to form an imine. But in the case of the arylation of sulfoximines, it should proceed with retention of configuration at a chiral sulfur atom since no proton is available at that position (β-position of coordinated palladium). Since Bolm's group has been involved in the synthesis of C_1-sulfoximines as ligands (Type **B**, Figure 19), they investigated the stereochemical path of the reaction of sulfoximine ***(R)*-2** and the oxazoline ***(S)*-51** (Scheme 73).

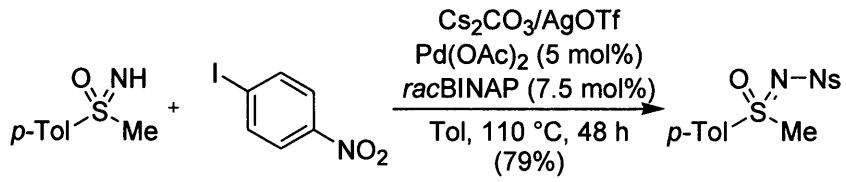
Under the standard reaction conditions (Scheme 70) or slightly modified ones, *i.e.* using an excess of one of the coupling partners, the substituted sulfoximine product ***(R,S)*-52** was obtained in moderate yield (54-61%). However, using DPEphos as ligand and equimolar amounts of oxazoline ***(S)*-51** and sulfoximine ***(R)*-2**, the yield of product ***(R,S)*-52** reached 86% (Scheme 73).



Scheme 73

Palladium-catalysed coupling using aryl iodides was also investigated. The standard conditions applied were the same as for the palladium coupling with aryl bromides but the procedure using aryl iodides required the addition of lithium bromide or silver triflate (2 eq.) to be effective (Scheme 74).

Unfortunately, these conditions were not as reproducible as those used for the coupling with aryl bromides, and required optimisation for each substrate.



Scheme 74

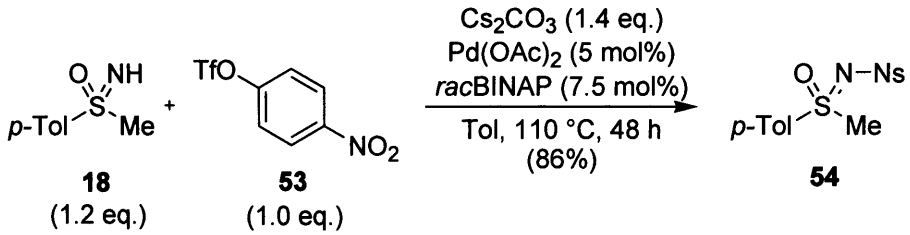
At the same time, Bolm worked on an extension of this methodology, first using aryl triflates (Scheme 75) or nonaflates (Scheme 76) in palladium-catalysed coupling, then nickel-catalysed coupling of sulfoximines with aryl tosylates (Scheme 77).[104]

Palladium-catalysed processes which employed aryl sulfonates were attractive because they are easily accessible from the corresponding phenols thus allowing an entirely different class of substrates other than aryl halides to be used as starting materials. During

studies on palladium-catalysed synthesis of arylamines, Buchwald found out that the use of cesium carbonate as a base instead of sodium *tert*-butoxide led to both an increase of functional group tolerance and a strongly decreased rate of hydrolysis of the triflate precursors.[105]

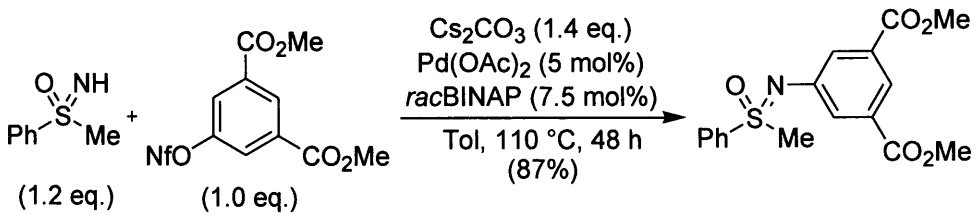
Compared to aryl triflates, the corresponding nonaflates were even more attractive substrates because they display a higher reactivity and they are more stable towards hydrolysis.[106]

However, despite all these positive characteristics, at the time Bolm decided to apply this methodology to the coupling with *NH*-sulfoximines, palladium-catalysed aminations of aryl sulfonates with sp^2-hybridised nitrogen were still rare.



Scheme 75

Reactions of aryl triflates with sulfoximines under essentially the same conditions used for the couplings of aryl bromides, led to the corresponding products in high yields (51-86%). Interestingly product **54** was obtained with the highest yield (86%) and was achieved using sulfoximine **18** and 4-nitrophenyl triflate **53** (Scheme 75), which is the most susceptible substrate towards hydrolysis, indicating then that the latter was no important side reaction.



Scheme 76

Similarly to the reaction of aryl triflates, electron-deficient aryl nonaflates gave the highest yields (Scheme 76).

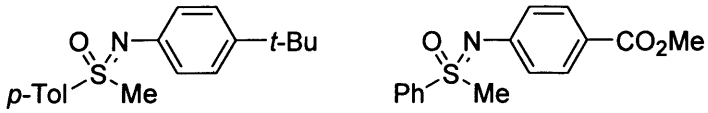
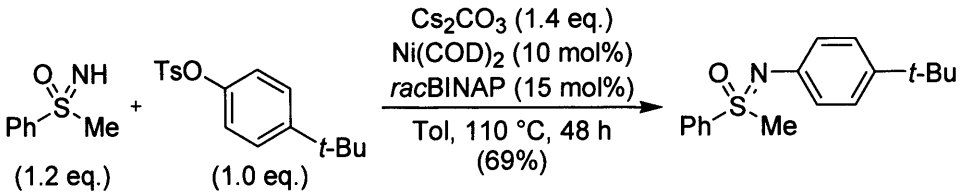


Figure 18

Using palladium-catalysed coupling *N*-(4-*tert*-butylphenyl)-*S*-methyl-*S*-(*p*-tolyl) sulfoximine was obtained in 76% yield with 4-*tert*-butylphenyl nonaflate and 67% yield with the corresponding aryl bromide (Figure 18). In the same way, *N*-[4-(methoxycarbonyl)phenyl] *S*-methyl-*S*-phenyl sulfoximine was obtained in an excellent yield (97%) which was again higher than that obtained in the coupling with the corresponding aryl bromide (90%).

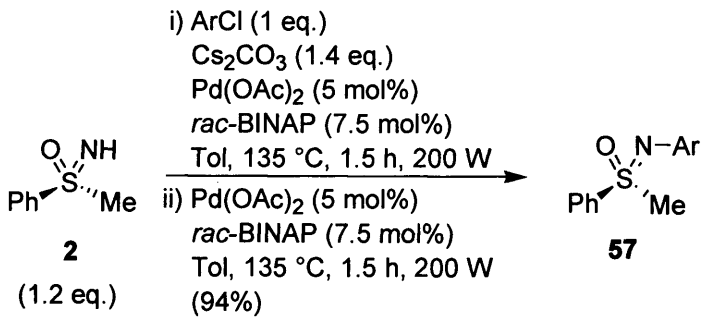


Scheme 77

Attempts to use aryl tosylates, less reactive species, in palladium-catalysed amination failed; however, changing the metal source to a nickel complex increased the catalytic activity notably (Scheme 77).

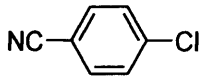
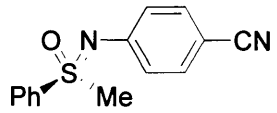
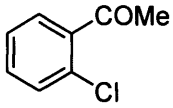
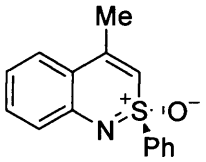
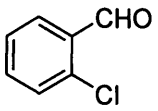
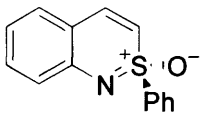
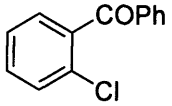
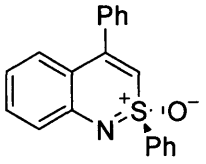
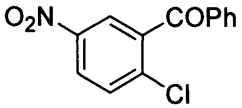
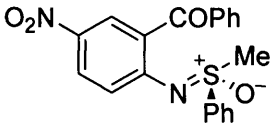
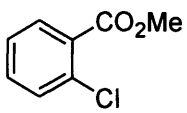
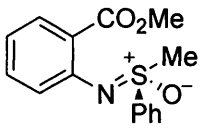
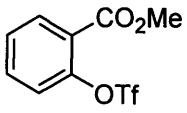
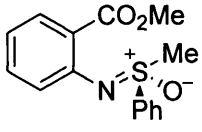
In 2004, Harmata developed a modified version of Bolm's coupling using aryl chlorides in a microwave-assisted reaction (Scheme 78).[107]

The coupling procedure is the irradiation at 200 W of a solution of *(R)*-methyl phenyl sulfoximine **2** (1.2 eq.), aryl chloride (1 eq.) and cesium carbonate (1.4 eq.) in the presence of palladium diacetate (5 mol%) and *rac*-BINAP (7.5 mol%) in toluene at 135 °C for 1.5 hours. Then second addition of the catalyst system - palladium diacetate (5 mol%) and *rac*-BINAP (7.5 mol%) - followed by another 1.5 hours irradiation in the same conditions.



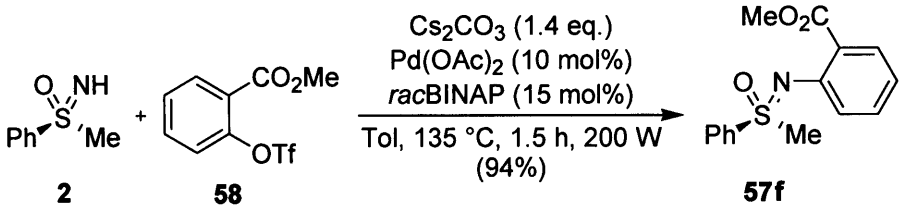
Scheme 78

Table 15

Entry	*Aryl Chloride*	*Product*	*Product Number*	*Yield (%)*
a			**57a**	94
b			**57b**	31
c			**57c**	87
d			**57d**	74
e			**57e**	90
f			**57f**	46
g			**57g**	94

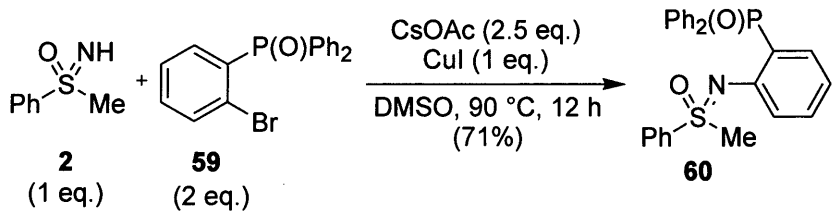
The authors focused mainly on electron-deficient aryl chlorides because they anticipated that these deactivated aromatic rings would react better in coupling reactions and some of them could be converted to benzothiazines (Table 15). That was indeed the case and using appropriate substrates, benzothiazines could be synthesised in a one-pot procedure (Entries b-d). In the standard reaction conditions, the coupling afforded the corresponding *N*-aryl sulfoximine **57a** in 94% yield (Entry a).

Interestingly, the nitrated analogue of 2-chlorobenzophenone (Entry e) gave only the corresponding *N*-arylsulfoximine **57e** albeit with really good yield (90%). One notable exception to the high yields was the synthesis of ester **57f** from methyl 2-chlorobenzoate (Entry f) which proceeded in only 46% yield using the standard irradiation procedure for the coupling. When the starting material was replaced by the corresponding triflate **58** (Entry g, Scheme 79) and the procedure modified, ester **57f** was obtained in 94% yield.



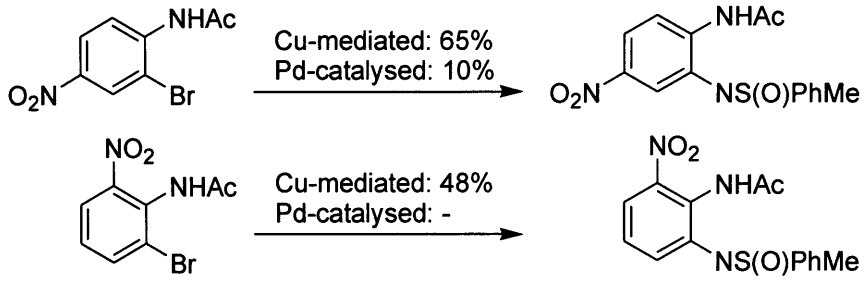
Scheme 79

Despite the success of palladium-catalysed cross-coupling, some limitations such as long reaction times, restricted substrate scope, and high cost of the catalyst system, have motivated the search for another cross-coupling protocol. During the last years, copper-mediated or -catalysed carbon-heteroatom couplings have been developed by several groups after studies independently initiated by Chan,[108] Evans,[109] and Lam.[110] Based on the recent work on copper-promoted C-N bond formation,[111, 112] copper-mediated cross-coupling for the synthesis of *N*-aryl sulfoximines was investigated by Bolm.[113] Numerous sulfoximines were successfully *N*-arylated (48-95% yields) by coupling with aryl iodides or aryl bromides, in the presence of an equimolar amount of copper iodide and cesium acetate or cesium carbonate in DMSO (Scheme 80).



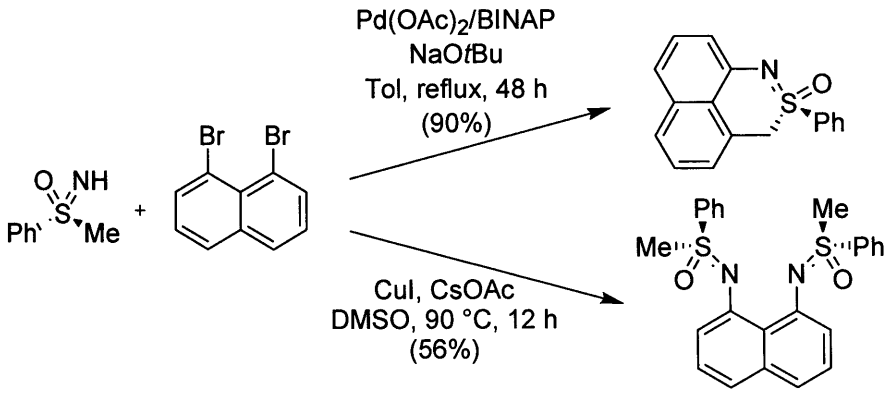
Scheme 80

With palladium catalysis sulfoximine **60** was formed in low yield and was contaminated by inseparable impurities, but **60** can be formed in a straightforward manner with the copper-mediated method. Copper-mediated C-N coupling was found to be efficient with substrates that did not react under palladium catalysis or gave low yields, as was the case for rather highly functionalised aryl halides that were then converted to the corresponding sulfoximines in respectable yields (Scheme 81).



Scheme 81

Another interesting difference between the two routes is the possibility, with copper mediation, to synthesise bissulfoximidoyl products (Scheme 82).



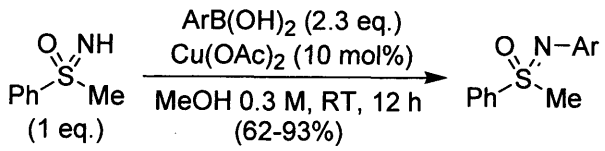
Scheme 82

The importance of C_2-symmetric bissulfoximines as ligands in asymmetric synthesis has been established and this new copper-mediated route offers a direct method for their synthesis.

As discussed earlier in the report, *N*-aryl sulfoximines offer great possibility as chiral ligands in asymmetric catalysis, especially those with a rigid backbone for which *N*-arylation reactions often are the key step of their synthesis. Both methodologies based on palladium and copper catalysis were developed by Bolm and Harmata for this purpose. Common characteristics of these protocols are the use of aryl halides (aryl triflates and aryl nonaflates can also be used in palladium-catalysed coupling) and the need for a base such as sodium tert-butoxide or cesium carbonate at high temperature. With the idea to extend the scope of substrates to *umpolung* aryl sources, Bolm developed a copper-promoted *N*-arylation of sulfoximines that uses boron reagents.

In 2003, Lam showed that *N*-arylations of α-aminoesters with *p*-tolylboronic acid proceeded with almost complete retention of configuration (94-99% *ee*).[114] In 2004, Xie demonstrated the use of boronic acid for the *N*-arylation of imidazoles, sulfonamides, imides, amines and amides in refluxing methanol without the need of an additional base.[115, 116] Both studies have given rise to interesting work by Bolm on a mild copper-catalysed *N*-arylation of sulfoximines with aryl boronic acids under base free conditions (Scheme 83).[117]

Several *N*-aryl sulfoximines were obtained in average to good yields (62-93%) and in all cases, these optimised reaction conditions were applicable (Table 16).



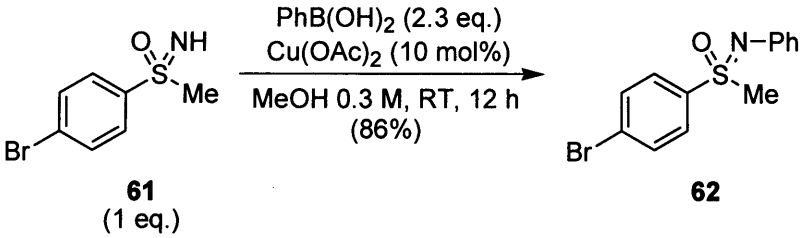
Scheme 83

Table 16

Entry	*Ar*	*Yield (%)*
a	2-Me-Ph–	75
b	4-Me-Ph–	92
c	2-Cl-Ph–	90
d	4-Cl-Ph–	93
e	4-(TBS)O-Ph–	88
f	2-naphthyl–	62
g	mesityl–	-

Good results were achieved with *para*-substituted aryl boronic acids (Entries b, d, e) and the same behaviour was observed with *ortho*-substituted aryl boronic acids albeit in this case yields were slightly lower (Entries a, c, f). This difference indicated the importance of steric effects in this cross-coupling reaction, while one substituent in the *ortho* position was a suitable substrate, 2,4,6-trimethylphenyl boronic acid failed to give the corresponding *N*-aryl sulfoximine (Entry g).

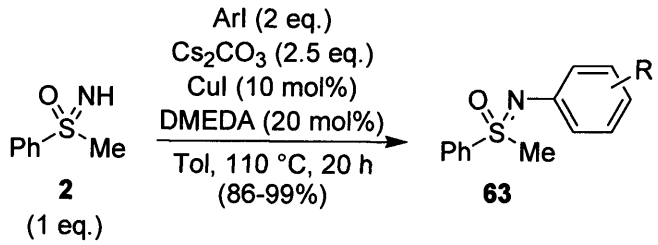
An interesting chemoselectivity was observed when sulfoximine **61** was utilised in a cross-coupling reaction with phenyl boronic acid (Scheme 84). Despite several reaction sites available for this coupling, only product **62** was formed in 86% yield.



Scheme 84

This result reveals that the *N*-coupling process is favourable over possible *C*-arylations, both at the aryl as well as the methyl group of the sulfoximine moiety. Furthermore, it allows further functionalisation of the resulting *N*-aryl sulfoximine through the remaining bromine attached to the aryl group.

The next step was reached in 2005 when a catalytic version of the copper-promoted method was developed in the same group.[118] This copper-catalysed coupling can either be used with aryl iodides (Scheme 85, Table 17) or with aryl bromides (Scheme 86).
Reaction conditions for the cross-coupling were optimised with sulfoximine **2** and iodobenzene (Entry a) to finally give a general protocol using a mixture of sulfoximine (1 eq.), aryl iodide (2 eq.), cesium carbonate (2.5 eq.), copper iodide (10 mol%) and DMEDA (2 mol%) in toluene at 110 °C. Several *N*-aryl sulfoximines were then synthesised in excellent yield.



Scheme 85

Table 17

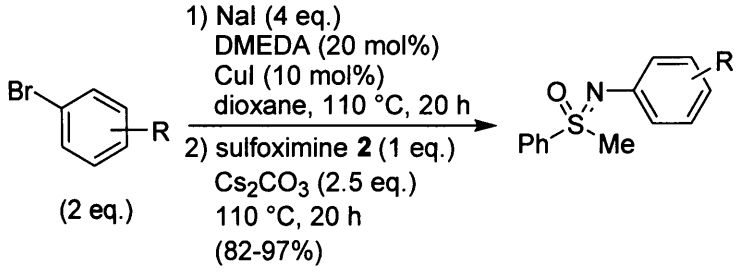
Entry	*Aryl iodide substituent R*	*Product*	*Yield (%)*
a	H	**63a**	95
b	2-NO_2	**63b**	93
c	3-NO_2	**63c**	98
d	4-NO_2	**63d**	92
e	2-OMe	**63e**	99
f	3-CN	**63f**	99
g	2-P(O)Ph_2	**63g**	86

The substituent position did not appear to have any effect (Entries b-d) as the various nitro-substituted iodides formed the corresponding sulfoximines in more than 92% yield. The same observation was made regarding for the electronic effects of the substituent on the arene, as 2-nitro and 2-methoxy substituted iodides afforded products **63b** and **63e** in respectively 92 and 99% yields (Entries b, e). Steric hindrance seemed to have an impact, but even an iodide bearing a bulky phosphorus substituent in the *ortho*-position formed the corresponding sulfoximine **63g** in 86% yield (Entry g).

The other copper-catalysed coupling procedure developed used aryl bromides as aryl sources, but all attempts to apply the previous conditions failed. The problem was circumvented by using Buchwald's aromatic Finkelstein reaction. However, this reaction

does not tolerate the presence of both cesium carbonate and sulfoximine; consequently a one-pot-two-step procedure was developed (Scheme 86, Table 18).

The coupling reaction between sulfoximine **2** and bromobenzene (Entry a) was the standard reaction used for the optimisation of the procedure and the corresponding product was formed in 93% yield. The best results were achieved by keeping a mixture of aryl bromide (2 eq.), copper iodide (10 mol%), DMEDA (20 mol%) and sodium iodide (4 eq.) in dioxane at 110 °C for 20 h, then adding base (2.5 eq.) and sulfoximine (1 eq.) and stirring at 110 °C for a further 20 h.



Scheme 86

Table 18

Entry	*Aryl bromide substituent R*	*Yield (%)*
a	H	93
b	2-Me	93
c	2-MeO	97
d	4-MeO	84
e	2-F	86

The authors observed that compared to coupling with aryl iodides (Table 17), the yields in the transformation of aryl bromide (Table 18) were slightly lower. That could be because of the one-pot-two-step procedure, compared to the one-step reaction with aryl iodide, and also the use of dioxane, which is known to be a less effective solvent for *N*-arylation.

1.2.7.3. Conclusion

In 2002, Bolm and his group published a mild procedure for the alkylation of sulfoximines which represented the beginning of the fruitful investigation on the derivatisation of *NH*-sulfoximines. Acylation of the latter with acyl chlorides followed by reduction with of the intermediate with borane species, allowed the access to *N*-alkyl sulfoximines, ethylene-bridged bissulfoximines used as potential ligands and new pseudopeptides. *N*-Vinyl sulfoximines, unreported before Bolm's work, are now available in high yields by palladium-coupling with vinyl bromides or triflates; the resulting *N*-vinyl sulfoximines can be reduced by hydrogenation to give the corresponding *N*-alkyl sulfoximines. The copper-catalysed *N*-vinylation of free sulfoximines is also efficient, and in contrast to the palladium-catalysed version, this procedure is cheaper and tolerates bulky substrates or vinyl bromides.

The development of new methods to access *N*-aryl sulfoximines were based on metal-catalysed coupling of *NH*-sulfoximines with various halides; again palladium-catalysed arylation with aryl bromides, iodides, triflates or nonaflates, was the first general method to facilitate the access to *N*-aryl sulfoximines. In the same time, the development of a nickel-catalysed arylation using tosylates as coupling partners was successful and a modification of this method by Harmata led to another efficient palladium-coupling using aryl chlorides. Copper mediated coupling methods were investigated in response to the significant drawbacks related to the use of palladium (high cost of the catalyst and phosphine ligands, long reaction time and limited substrate scope).

Here as well, this field was pioneered by Bolm and his group who developed a copper-promoted coupling of free sulfoximines with aryl bromides. Comparison between the two methods showed that the copper-mediated procedure had a better tolerance toward the type of aryl bromides suitable for this coupling; this method also allowed the synthesis of bissulfoximines by coupling with dibromoarenes. The coupling of *NH*-sulfoximines with aryl boronic acids in the presence of copper diacetate also provided an efficient arylation method under base free conditions; an interesting chemoselectivity was observed, when different reaction sites were available only the *N*-arylation took place. In a catalytic version

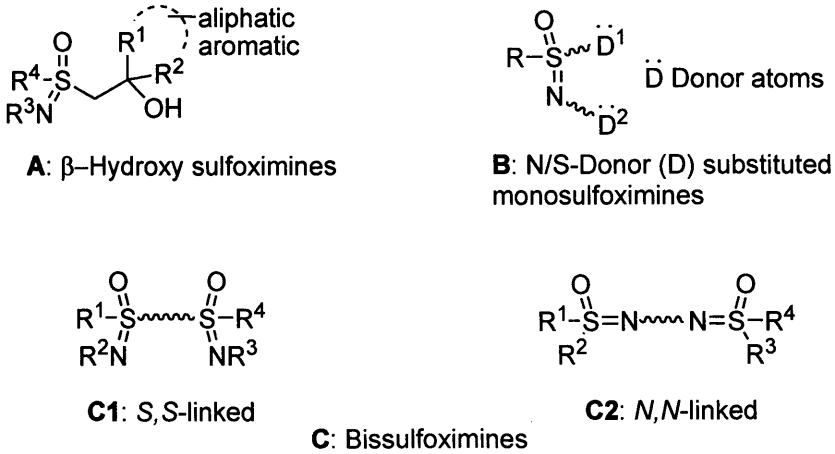
of copper-promoted arylation first reported by Bolm, coupling with aryl bromides or iodides afforded the corresponding *N*-aryl sulfoximines in high yields with only a difference in the procedure.

Finally, the methods now available use mild conditions compared to the classical procedures which necessitated harsh conditions for a limited substrate scope. However, all methods cited previously except for the *N*-acylation, are metal-catalysed, and in the context of decreasing the toxicity of organic synthesis methods, there is still room for improvement.

1.3. Sulfoximines as chiral ligands

The synthesis of optically active compounds as pure enantiomers, using catalytic amount of chiral, non-racemic additives is a major challenge in organic chemistry. Therefore, sulfoximines with their donor atoms directly on the chiral sulfur atom, should be well established as chiral ligands. However, before the early 1990s, when Bolm started to investigate this research area, only Johnson and Stark had reported in 1979 the use of chiral sulfoximines in an asymmetric transformation.[119]

The analysis of sulfoximines synthesised as ligands to date leads to the classification into three structural types depicted in Figure 19.



A: β–Hydroxy sulfoximines

B: N/S-Donor (D) substituted monosulfoximines

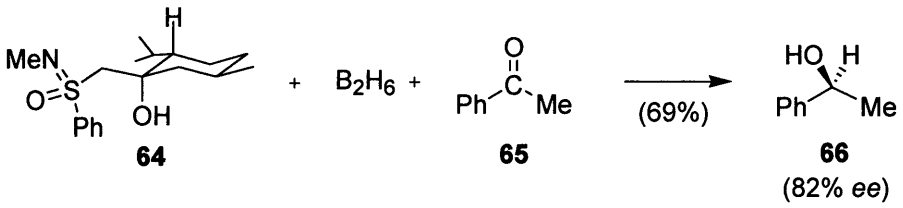
C1: *S,S*-linked

C2: *N,N*-linked

C: Bissulfoximines

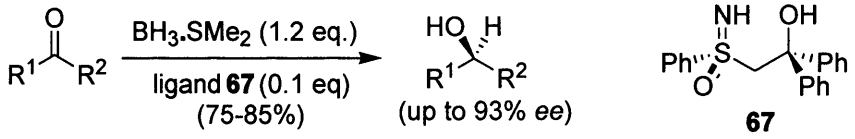
Figure 19: sulfoximines ligands

Treatment of enantiomerically pure β-hydroxy sulfoximine **64** (Type **A,** Figure 19) with diborane led to the formation of a chiral complex that reduced acetophenone **65** to the corresponding *(S)*-configured alcohol **66** in 69% yield and 82% *ee* (Scheme 87).[119]



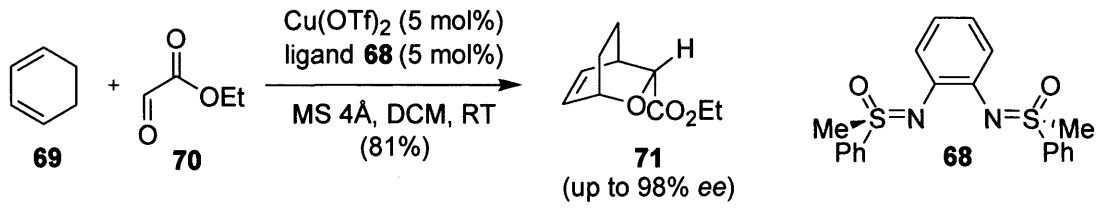
Scheme 87

Fourteen years later Bolm *et al.* used β-hydroxy sulfoximine **67** (Type **A**, Figure 19) in catalytic asymmetric reductions of ketones with borane-DMS complex (1.2 eq.) as the hydride source, to afford the corresponding secondary alcohols as the only observed products in high yields (75-85%) with good enantiomeric excesses (up to 93% *ee*) (Scheme 88).[120]



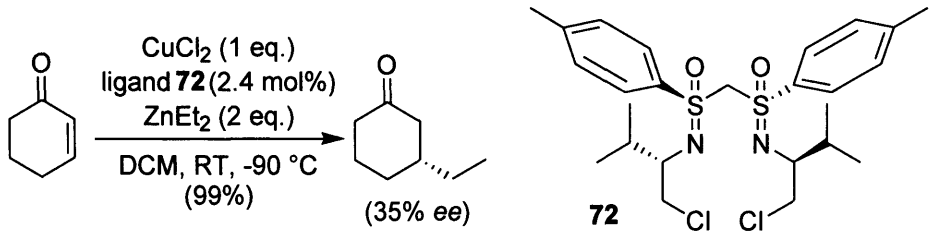
Scheme 88

At the end of the 1990s, only a few metal/sulfoximine complexes could compete with existing systems for a given catalysis, but in 2001 Bolm obtained excellent result with a C_2-symmetric sulfoximine (Scheme 89). Copper-catalysed hetero-Diels-Alder reaction between cyclohexadiene **69** and ethyl glycolate **70**, with *N,N*-bissulfoximine **68** (Type **C2**, Figure 19), gave the product **71** in 81% yield and up to 98% *ee*.[121]



Scheme 89

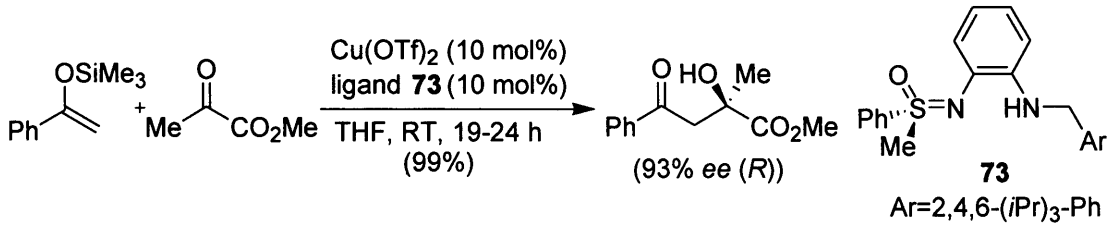
In 2004, Reggelin published a synthesis of *S,S*-linked bissulfoximines (Type **C1**, Figure 19), of which only two racemic examples had ever been synthesised before,[122, 123] and investigated their use in boron-mediated reduction and in 1,4-addition reactions (Scheme 90).[124]



Scheme 90

In the first model reaction, reduction of acetophenone with borohydride-THF complex (1 eq.) in the presence of a boron/*S,S*-linked bissulfoximine complex in toluene, gave the corresponding alcohol in moderate (58%) to quantitative yields but only 28-48% *ee* was achieved; studies on 1,4-addition reactions to cyclohexenone produced similar levels of selectivity and average yields mostly (48-99% yields, 7-35% *ee*). Despite the selectivity of this system being rather low, its reactivity was high and given the many ways for constitutional and configurational changes, *S,S*-linked bissulfoximines such as **72** seem to be promising chiral ligands.

In 2005, Bolm described the synthesis of C_1-symmetric aminosulfoximines (Type **B**, Figure 19) and their use as ligands in copper-catalysed asymmetric Mukaiyama-aldol reactions (Scheme 91).[125]



Scheme 91

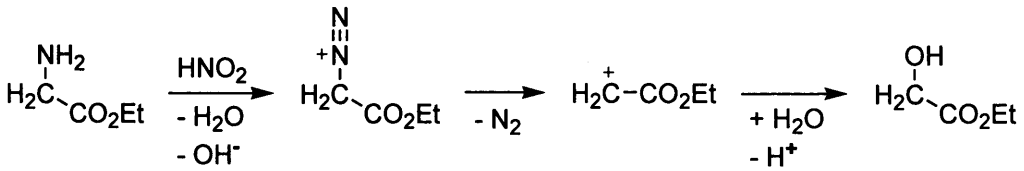
Under these optimised conditions, several β-hydroxyketones were synthesised in 44-90% yields, with 67-99% *ee*.

In conclusion, the use of sulfoximines as ligands has only recently been studied in greater detail, and the initial results are promising of a high potential of these chiral sulfur reagents in catalytic asymmetric synthesis. The recent development of their preparative methods allow them now to be synthesised in enantiopure form on a large scale, and with this improved accessibility new applications in sulfoximine-based catalytic reactions can emerge.

1.4. Chemistry of sulfur-containing carbenes

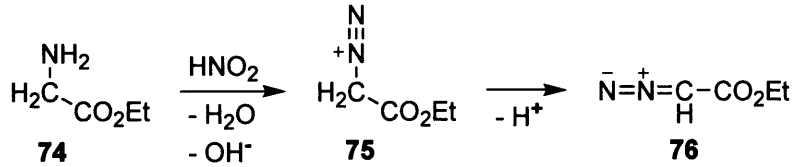
1.4.1. Diazo compounds:introduction

The beginning of diazo chemistry is generally dated to 1858 when Griess discovered and identified the first aromatic diazonium ion; however transient diazonium ions had been obtained by Piria ten years before the discovery of Griess, but it took many years until their formation was established. Piria found that, by treating aliphatic amines with nitrosating reagents in water, the amino group was replaced by a hydroxy group (Scheme 92).



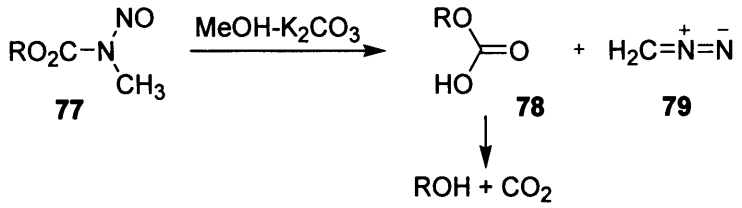
Scheme 92

The first aliphatic diazo compound was isolated much later, namely by Curtius in 1883, who synthesised diazoacetate **76** by reaction of aminoacetate **74** with nitric acid (Scheme 93).[126]



Scheme 93

Diazomethane **79**, the simplest member of diazoalkanes series, was first obtained by von Pechmann in 1894 from *N*-methyl-*N*-nitroso carbamate **77** in diethyl ether with methanol and potassium carbonate (Scheme 94).



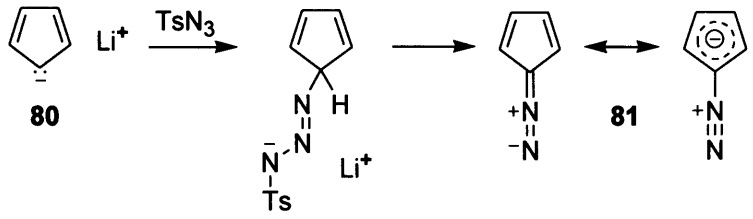
Scheme 94

In contrast to aromatic diazo compounds, diazoalkanes are less important as large-scale industrial intermediates. Nevertheless reactions inducing the loss of dinitrogen molecule offer a series of important applications in organic synthesis, since Wolff in 1902 discovered the rearrangement of diazoketones into carboxylic acids. After modifications, this reaction became three decades later the key to the Arndt-Eistert method for the preparation of homologous carboxylic acids.

Since the 1950s and 1960s when organic compounds with heteroatom enjoyed increasing interest, the use of sulfonyl and phosphoryl diazo compounds for synthetic purposes became a frequent entry to sulfur, phosphorus and other organic compounds substituted with less common groups. In 1888, Buchner investigated the reaction of diazoacetate with fumaric acid; without realising it, this reaction was the first 1,3-dipolar cycloaddition. In

the case of aromatic diazonium compounds, they became industrially very important after Griess discovered in 1861-1862 the azo coupling reaction, by which the first azo dye was made by C. A. Martius in 1865. This is still the most important industrial reaction of diazo compounds.[127]

The first scientist who carried out a diazo transfer reaction was Dimroth in 1910, the process was rediscovered by Curtius and Klavehn in 1926 and finally by Doering and DePuy, who reported in 1953 the first synthesis of a diazo compound by diazo transfer; reaction of cyclopentadienyl anion **80**, a very strong nucleophile formed from cyclopentadienyllithium and tosylazide, afforded diazocyclopentadiene **81** (Scheme 95).[128]

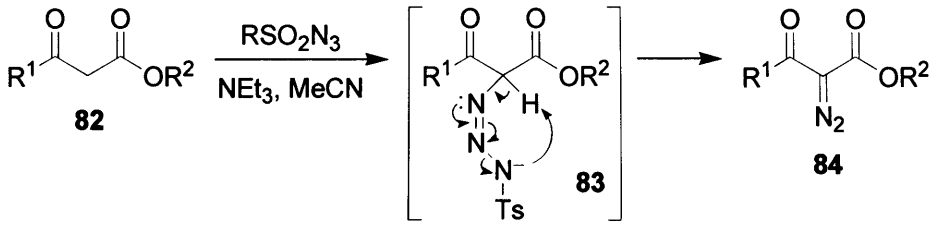


Scheme 95

However none of them realised at that time the general applicability of this reaction. Later, Weil and Cais in 1963 and subsequently Regitz and Liedhegener in 1966, found that in this reaction phenyllithium can be replaced by almost any base and extended the practicability of this procedure.

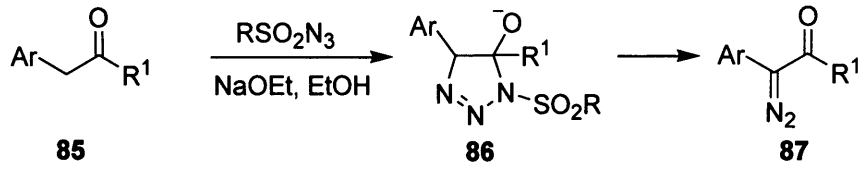
1.4.2. Diazo transfer and synthesis of α-diazosulfones

The standard procedure for diazo transfer reaction, introduced in 1966 by Regitz and co-workers,[129] consisted of the transfer of a complete diazo group from a donor, usually a sulfonyl azide, to an acceptor, substrate having a doubly activated methylene group (Scheme 96).[130]



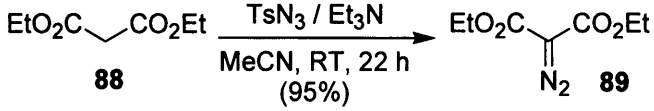
Scheme 96

Diazoesters **84** are formed almost quantitatively from β-dicarbonyl compounds of type **82**, β-keto esters or malonic esters (R^1=OR), by transfer of diazo groups in acetonitrile/triethylamine, in which intermediates **83** are conceivable. When aryl-activated methylene compounds **85** react with sulfonyl azide in alkaline solution, diazoketones **87** are formed through an triazoline intermediate **86** (Scheme 97).



Scheme 97

If the diazo transfer reaction on β-dicarbonyl compounds **82** is carried out in ethanol/sodium ethoxide medium, diazo-*N*-sulfonylcarboxamides are formed probably by way of the triazoline followed by the loss of an alkoxy group. As an exemple of the efficiency of the diazo transfer method reported by Regitz *et al.*, reaction of diethyl malonate with tosyl azide in acetonitrile in the presence of triethylamine afforded the correponding diazo compound in 95% yield (Scheme 98).

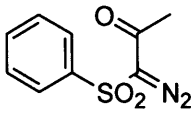


Scheme 98

Since this diazo chemistry has undergone extensive development, procedures now used are more flexible, various bases and azides can be used depending on the nature of the

substrate undergoing the reaction. Although several other safer reagents have been described,[131] sulfonyl azides are still the most commonly used.

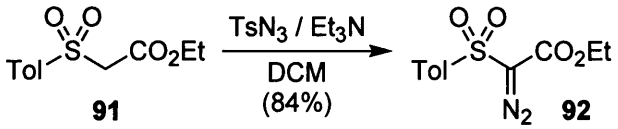
α-Diazo-β-ketosulfones were discovered in 1967 by Van Leusen and Strating with the synthesis of compound **90** (Figure 20) and were used as a source of α-sulfonylcarbenes.[132]



90

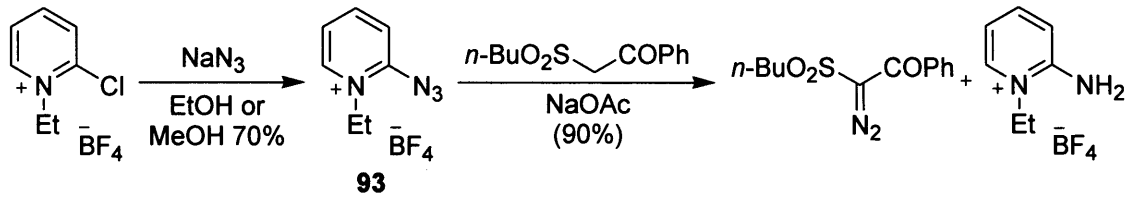
Figure 20

The carbon next to the sulfone moiety had to be activated by a second electron-withdrawing group (commonly a ketone or an ester) to achieve the diazo transfer.[133] For example, in similar reaction conditions than those described in 1967, the acetonitrile was changed for DCM, ethyl tosyldiazoacetate **92** was synthesised in 84% yield from **91** (Scheme 99).



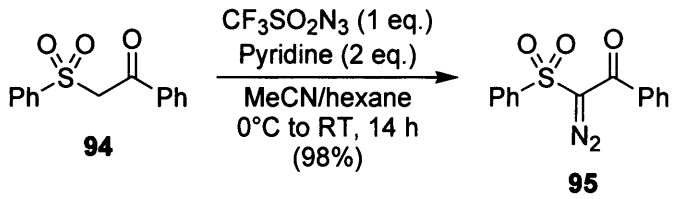
Scheme 99

The synthesis of azidinium salts was introduced by Balli *et al.* in 1961.[134] Several heterocyclic azidinium salts have been used to run efficient diazo transfer[135, 136] but this procedure required high cost reagents. This problem was solved in a 1987 paper by Monteiro, who developed another efficient and mild procedure, using azidinium salt **93** generated *in situ* from rather inexpensive chemicals under neutral conditions (Scheme 100).[137]



Scheme 100

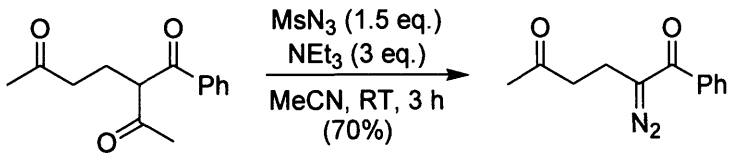
In 2000 Charette *et al.* reported another efficient diazo transfer using trifluoromethanesulfonyl azide in acetonitrile in the presence of pyridine.[138] Under these reaction conditions, diazo sulfone **95** was obtained in 98 % yield (Scheme 101).[139]



Scheme 101

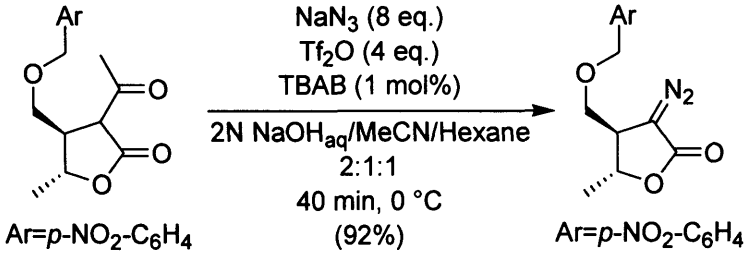
These authors also reported an optimisation of this system with respect to the base. It appears that there is a good correlation between the pKa of the conjugate acid and the yield of the diazo transfer. In the case of a highly electrophilic diazo compound, the use of a too strong base can lead to decomposition of the product and dramatically decrease the yield.

It is known that diazo transfer to a keto enolate is not a particularly efficient reaction.[140] Instead, generation of the diazo group is usually achieved by a "deacylation diazo transfer" strategy;[141-143] the peculiar behaviour of β-acetyl esters in diazo transfer reactions, leading to a deacylation, was first observed by Regitz in 1966.[130] This method consists of temporarily activating the carbon atom of the diazo transfer site with a carbonyl group, this auxiliary group, for example a formyl[144] or an acetyl[145], is removed during diazo transfer (Scheme 102).



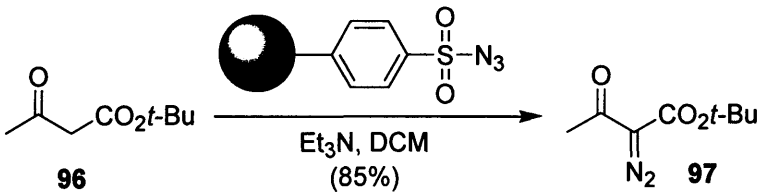
Scheme 102

In a slightly different procedure, Brown *et al.* followed the same strategy but in their case the diazo transfer is achieved by *in situ* formation of triflic azide, by reaction of sodium azide and triflic anhydride in the presence of 2M sodium hydroxide aqueous solution and a PTC (Scheme 103).[146, 147]



Scheme 103

The last diazo transfer procedure that will be reported here is both efficient and safe, this method is based on the reaction with polystyrene-supported azide (Scheme 104).[148]



96 **97**

Scheme 104

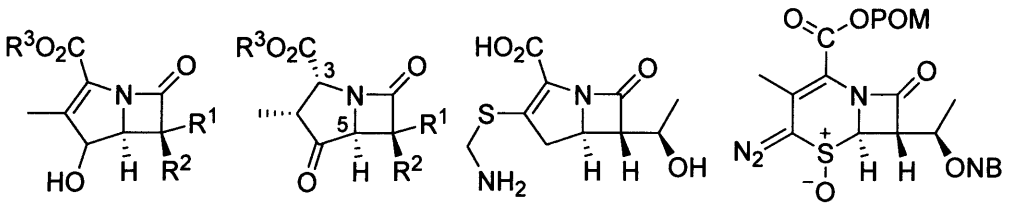
Diazo compound **97** was obtained in 85% yield using polystyrene-supported azide, and in 76% yield using a sulfonyl azide in solution, *p*-CBSA.

1.4.3. Applications of sulfur-containing carbenes

Applications of diazoesters and diazoketones in organic synthesis are well established and documented. In this section, we will focus on synthetic uses of the less widely used sulfur-containing diazo compounds.

1.4.3.1. Photorearrangement of α-diazosulfoxides

The first example of an utilisation of a sulfinyl carbene is a rearrangement of a α-diazosulfoxide. In 1990, Rosati *et al.* reported the preparation of a diazo cephalosporanate sulfoxide precursor **101** as a key intermediate, in a convenient synthesis of carbapenem **98** and carbapenam **99** (Figure 21).[149] The carbapenem class of antibacterials finds use in the treatment of bacterial infections where the infective agent has built up a partial resistance to conventional antibiotics of the penicillin class; these compounds are based on the thienamycin structure **100**.

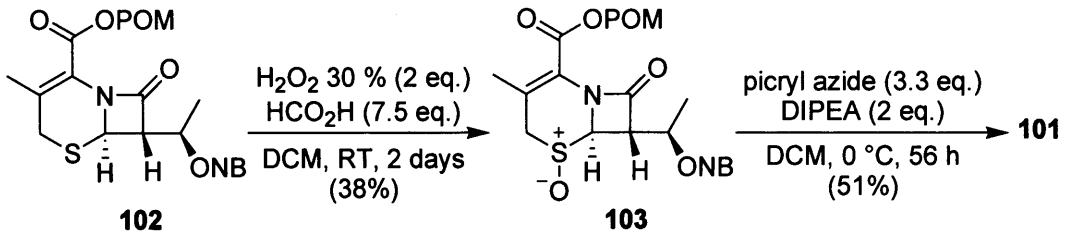


98 Carbapenem | **99** Carbapenam | **100** Thienamycin | **101** Diazo cephalosporanate sulfoxide precursor

Figure 21

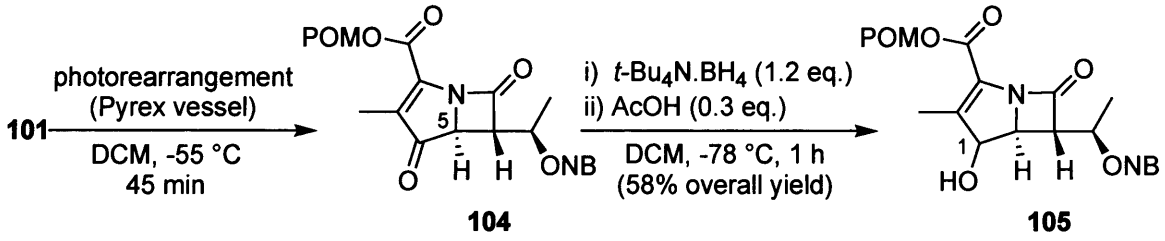
The synthesis of precursor **101** is depicted in Scheme 105 starting from the sulfide **102**. Oxidation of the latter with a mixture of hydrogen peroxide and formic acid in DCM led, after two days to a mixture of diastereomers α-sulfoxide and β-sulfoxide **103** (major isomer) in 38% yield; these two sulfoxides had to be separated since the corresponding α-sulfoxide is resistant to diazo transfer. Initial oxidation experiments on **102** employing the more sterically demanding *m*-CPBA resulted in a mixture containing a higher proportion of the undesired α-sulfoxide. Diazo transfer on pure β-sulfoxide with picryl azide in the

presence of DIPEA afforded the corresponding diazo cephalosporanate sulfoxide precursor **101** in 51% yield.



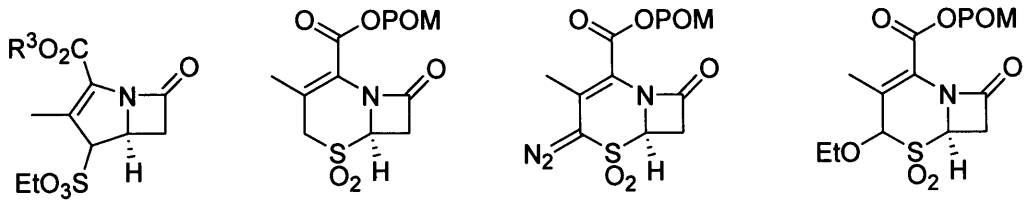
Scheme 105

The photorearrangement of the sulfinyl carbene derived from diazosulfoxide **101** was a "Wolff-type" rearrangement with retention of configuration at C-5 (Scheme 106). The reaction apparently proceeds with retention of configuration at the migratory center to afford an intermediate sulfine, which in a facile second step extrudes sulfur monoxide to give the isolated enone **104**. Because of its lability at room temperature, enone **104** was immediately reduced with tetrabutylammonium borohydride at -78 °C to afford one diasteromeric carbapenem alcohol **105** of undetermined configuration at C-1.



Scheme 106

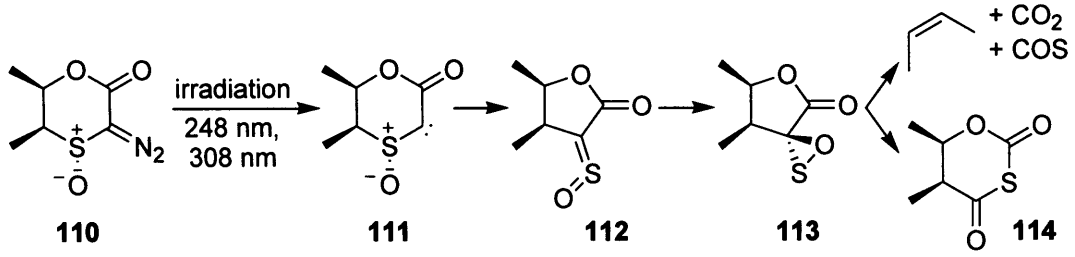
If diazo sulfones were to photorearrange analogously, carbapenemsulfonates **106** (Figure 22) might be produced. To test this possibility, cephalosporanate sulfone **107** was synthesised and by using the diazo transfer conditions used previously (picryl azide), was converted to diazo sulfone **108**; **108** is much more reactive than the corresponding sulfoxide and cannot be isolated. Ambient conditions are sufficient to decompose **108** in the presence of ethanol; unfortunately, the only isolated product **109** of this reaction arises from an insertion pathway.



106 Carbapenemsulfonate | **107** Cephalosporanate sulfone | **108** Diazo cephalosporanate sulfone | **109** O-H Insertion product

Figure 22

Recently, Maguire *et al.* reported the photochemical behaviour of α-diazosulfoxide **110** in argon matrix at 10 K (Scheme 107).[150]



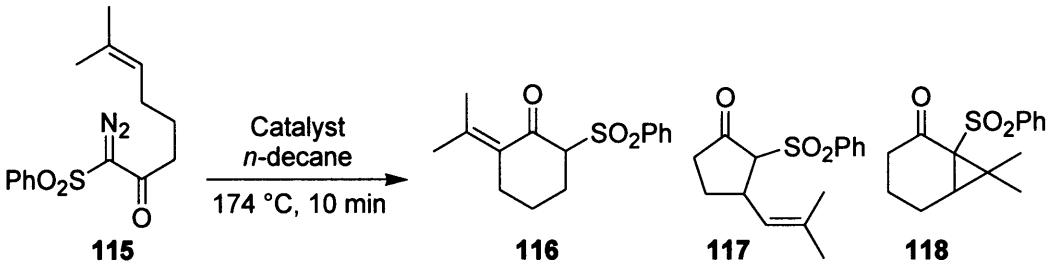
110 **111** **112** **113** **114**

Scheme 107

The first step on irradiation may be loss of nitrogen to form a carbene intermediate **111**; however, this species could not be isolated. Carbene **111** could then undergo a hetero-Wolff rearrangement to form the (*E*)-sulfine *E*-**112**, which itself undergoes photochemical rearrangement to form the oxathiirane **113**. Formation of this oxathiirane was also postulated in a related system based on experiments carried out by the authors but it was not detected in the matrix. Oxathiirane **113** reacts photochemically in two different ways. It either decomposes to form carbon dioxide, carbone oxide sulfide and *c*butene or it rearranges to form oxathianedione **114**. On irradiation at 248 nm, decomposition products predominate, whereas rearrangement products predominate on irradiation at 308 nm.

1.4.3.2. C-H insertions using a sulfonyl carbene

The first report related to the use of a sulfonyl carbene in a metal catalysed reaction dates from 1976, Kuwajima *et al.* investigated thermal and copper catalysed decomposition of some unsaturated acyclic α-diazo-β-keto phenylsulfones (Scheme 108).[151]

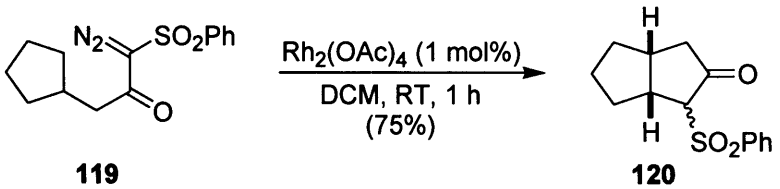


115 **116** **117** **118**

Scheme 108

They studied the formation of those three compounds - **116** derived from phenylsulfonylketene, **117** from the C-H insertion pathway of the corresponding ketocarbene and **118** is formed through the cyclopropanation reaction - and the influence of the reaction conditions on the yield of each product.

Monteiro has extended this reaction to intramolecular C-H insertions on saturated acyclic α-diazo-β-keto phenylsulfones to afford α-phenylsulfonyl cyclopentanones.[5] Diazo compound substrates were prepared by the mild diazo transfer procedure utilising azidinium salts described previously by the same author and used as crude materials. The reaction with substrate **119** involved catalytic amount of rhodium diacetate dimer (1 mol%) in DCM to give compound **120** in 75% yield (Scheme 109).

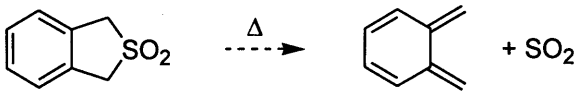


119 **120**

Scheme 109

In 1986 Durst *et al.* reported the rhodium catalysed decomposition of various α-diazo-β-phenylmethanesulfonyl esters resulting in intramolecular C-H insertions on aromatic systems.[152, 153] The goal was to prepare synthetically useful intermediates **121**, which

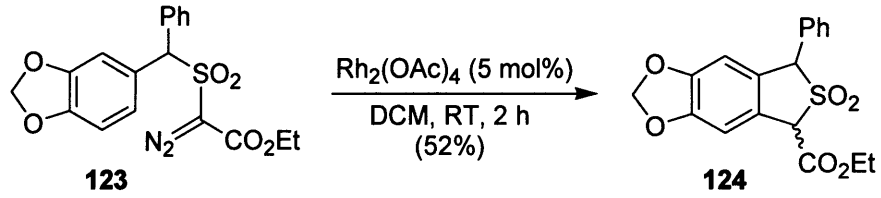
could undergo sulfur dioxide extrusion leading to useful *o*-quinodimethanes **122** (Scheme 110).



121 **122**

Scheme 110

Diazo sulfone **123** was obtained by diazo transfer with tosyl azide in the presence of sodium hydride in THF in 26% yield; the yields of the various steps needed to synthesise the starting materials were generally good except for the diazo transfer reaction, which rarely afforded the desired product in higher than 50% yield despite extensive variations in the reaction conditions (especially in respect to the base/solvent system). Cyclic sulfone **124** was synthesised in 52% yield by decomposition of diazo sulfone **123** catalysed by rhodium diacetate dimer (Scheme 111).

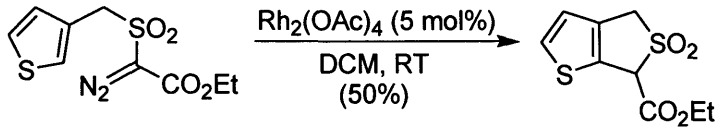


123 **124**

Scheme 111

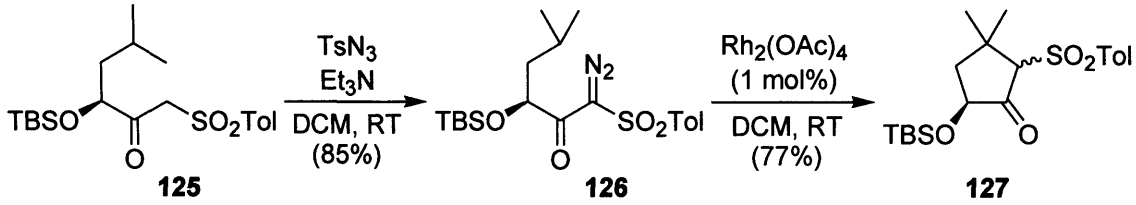
The authors found toward the end of the investigation that the use of rhodium bistrifluoroacetate significantly improved the yield, cyclic sulfone **124** was obtained in 74% yield using the new catalyst.

They also tried the rhodium catalysed intramolecular C-H insertion on other heteroaromatic systems such as indoles or thiophenes (Scheme 112); the C-H insertion failed when a furan derivative was used.



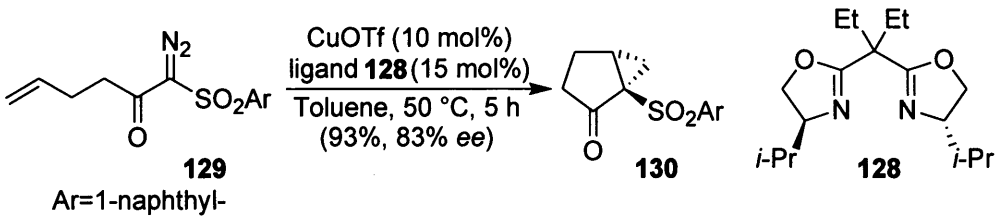
Scheme 112

In a program directed towards the synthesis of triquinane skeletons, Sengupta *et al.* identified the cyclopentanone derivative **127** as a key building block, in particular because of its dense functionalisation and an embedded *gem*-dimethyl substitution.[154] **127**-Type compounds promised to serve as a common intermediate for the synthesis of various sesquiterpenes and related natural products. After thorough investigation of the reaction conditions and various protecting groups, the synthesis of **127** was achieved by diazo transfer on β-ketosulfone **125** followed by rhodium-catalysed cyclisation of diazo sulfone **126**, according to the sequence depicted in Scheme 113.



Scheme 113

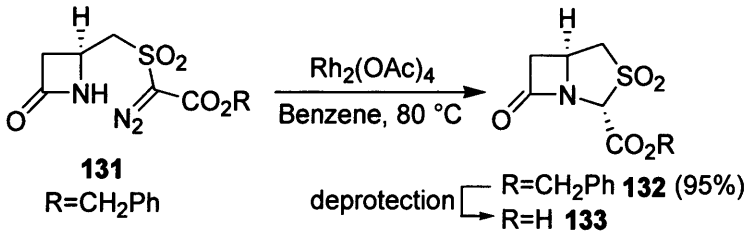
The last example of metal catalysed reaction of α-diazo-β-ketosulfone is from Nakada *et al.* in 2003, the authors studied the enantioselective intramolecular cyclopropanation catalysed by copper(I) triflate.[155] This investigation was followed three years later by its application to the asymmetric total synthesis of enantiopure (-)-methyl jasmonate,[156] starting from a new enantiopure chiral building block **130** prepared via the originally developed catalytic asymmetric intramolecular cyclopropanation reaction of α-diazo-β-ketosulfone **129** in 2003 (Scheme 114).



Scheme 114

1.4.3.3. Intramolecular rhodium carbenoid N-H insertions

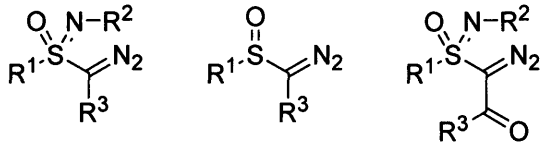
In 1983, Brennan *et al.* reported rhodium-catalysed N-H insertion of a sulfonyl carbene using methodology analogous to that described for the synthesis of a thienamycin-based skeleton (Scheme 115).[157, 158] The method here developed simplified the access to these potentially useful intermediates β-lactams **133**, the key step was the formation of the bicyclic skeleton. Decomposition of diazo compound **131** with rhodium diacetate dimer in benzene afforded ester **132** (R=CH_2Ph) in 95% yield; subsequent deprotection led to the synthesis of the target molecule **133** (R=H).



Scheme 115

2. Results and Discussion

The original aim of this project was to develop α-diazosulfoximines **134** (Figure 23) as chiral analogues of α-diazosulfones, and to test them in a variety of metal carbene reactions, with the goal of obtaining synthetically useful levels of diastereoselectivity.



134 **135** **136**

Figure 23

While numerous literature methods were available both for the synthesis of sulfoximines[16] and for the synthesis of α-diazosulfones,[1] α-diazosulfoximines were unknown at the commencement of the project.

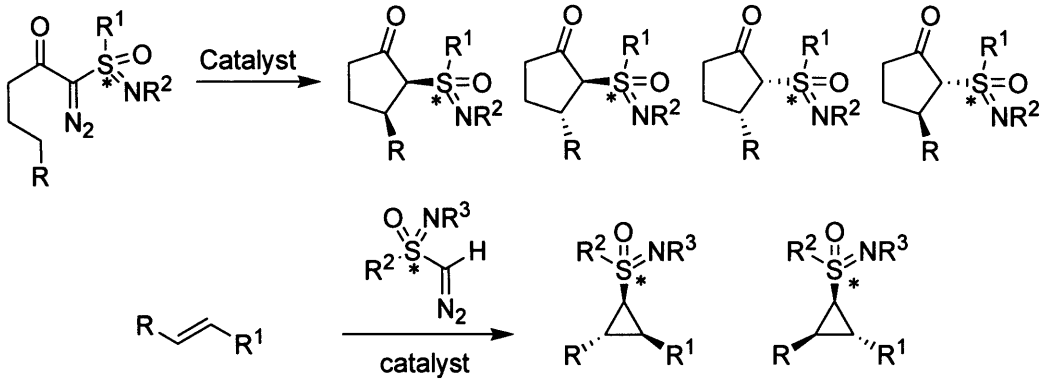
The most closely related literature chemistry involved α-diazosulfoxides **135** (Figure 23). Although a few examples of such compounds were known,[7] acyclic diazosulfoxides had been reported to be somewhat unstable by Maguire *et al.*,[9] while the cyclic analogues were considerably more robust. Further research on the low-temperature photochemistry of these species was reported by Maguire and Sander during the course of this project.[150]

2.1. Towards acyclic α-diazo-β-ketosulfoximines by diazo transfer

2.1.1. Initial work

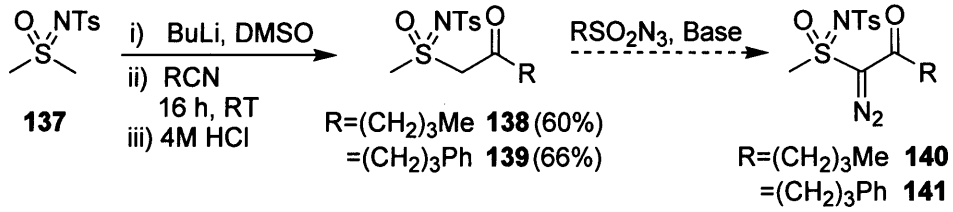
The first target compounds were simple acyclic α-diazo-β-ketosulfoximines such as **136** (Figure 23) in racemic form; our concept was that these could then be tested for diastereoselectivity in cyclopropanation or intramolecular C-H insertion reactions (Scheme

116). If these reactions proved successful, asymmetric synthetic routes could then be developed.



Scheme 116

Racemic β-ketosulfoximines **138** and **139** were prepared by the method of Johnson (Scheme 117);[122, 159] thus commercially available *S,S*-dimethyl-*N*-tosylsulfoximine **137** in DMSO was deprotonated with *n*-butyllithium and the resulting anion reacted with either valeronitrile or 4-phenylbutyronitrile. Following acidic hydrolysis of the intermediate imines, ketones **138** and **139** were obtained in moderate yields, respectively 60% and 65%.



137

R=$(CH_2)_3$Me **138** (60%)
=$(CH_2)_3$Ph **139** (66%)

R=$(CH_2)_3$Me **140**
=$(CH_2)_3$Ph **141**

Scheme 117

The conversion of ketones **138** and **139** to the corresponding diazo compounds **140** and **141** was first investigated proceeding according to a 1993 procedure from Davies *et al.*[160], in which *para*-acetamidobenzenesulfonylazide (*p*-ABSA) was used as diazo transfer reagent instead of the more conventional tosyl azide. The diazo transfer reaction with *p*-ABSA in the presence of triethylamine in acetonitrile at room temperature was unsuccessful, and examination of the crude mixture by ^{1}H NMR showed that significant

decomposition had occurred. The results of other procedures and reaction conditions that were tested on ketosulfoximine **139** are reported in Table 19.

Table 19: Diazo transfer experimentation.

Entry	Conditions	Results
a	Et_3N (3 eq.), *p*-ABSA (1.1 eq.) MeCN, RT, 0 °C or -15 °C	decomposition
b	Et_3N (1 eq.), *p*-ABSA (1.1 eq.) CD_3CN or $CDCl_3$, RT	decomposition after azide was added
c	Et_3N, K_2CO_3 or Pyridine (2 eq.), *p*-ABSA (2 eq.) DCM, RT	decomposition
d	Et_3N (2 eq.), *p*-CBSA (2 eq.) MeCN or DCM, RT	decomposition
e	Pyridine (2 eq.), *p*-ABSA (2 eq.) MeCN or DCM, RT	no reaction
f	NaN_3 (8 eq.), Tf_2O (4 eq.), TBAI (0.01 eq.) MeCN/Hexane/NaOH 2N (1/1/2), 0 °C	*in situ*-generated $CF_3SO_2N_3$,[147] decomposition

Following the procedure from Davies, the starting material was consumed in 45 minutes but no desired product was identified; increasing the reaction time did not have any effect, neither had the lowering of the temperature of the reaction (Entry a). Since all attempts to determine the composition of the crude mixture were unsuccessful, we decided to investigate the stability of the starting material in the reaction conditions before any modification to the procedure or the reagents was made (Entry b). Both β-ketosulfoximines had ^1H NMR signals corresponding to an AB system between the carbonyl and the sulfoximine groups (Figure 24).

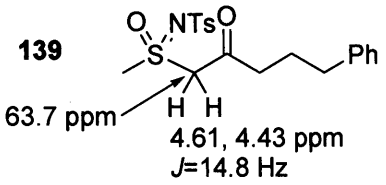


Figure 24

NMR experiments in which these signals were monitored, showed that ketosulfoximine **139** did not decompose upon treatment with base in the absence of a sulfonyl azide, but that decomposition occurred immediately on addition of the sulfonyl azide.

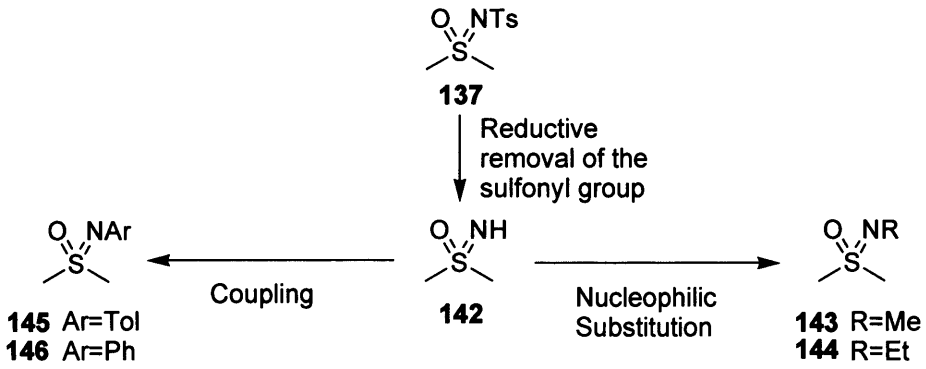
A range of bases (Entry c), diazo transfer reagents (Entries d, f), solvents (Entries d, e) and temperatures were investigated (Entry a).[9] All attempts to convert ketone **139** to the corresponding diazo compound **141** were uniformly unsuccessful. In all cases, while the starting material was consumed, none of the desired products were isolated. When *p*-ABSA was used, *p*-acetamidobenzenesulfonamide was tentatively identified in the crude mixture by the presence of a singlet at 2.15 ppm in the ^{1}H NMR spectrum, in addition to *p*-toluenesulfonamide which has a singlet at 2.10 ppm also present in the crude mixture. The identification of both sulfonamides suggested that diazo transfer had taken place but the resulting product **141** was unstable and decomposed. Unfortunately, no decomposition products corresponding to **139** could be isolated or identified, so no information about the decomposition pathway could be obtained.

Given the possibility that the sulfonamide group was being lost from the sulfoximine moiety, we decided to investigate the use of other nitrogen substituents.

2.1.2. Changing the substituent attached to the nitrogen atom

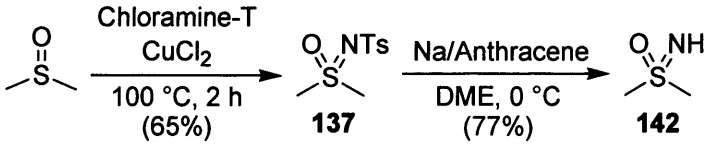
Since one of our interests in using the sulfoximidoyl moiety was the possibility to change the substituent attached to the nitrogen atom, thus altering the behaviour of β-ketosulfoximines during diazo transfer, several new substrates were prepared in the hope that this might lead to a more stable diazo compound. These substrates were accessible

from the key intermediate **142** either by nucleophilic substitution to synthesise *N*-alkyl sulfoximines **143** and **144**,[161] or by metal-catalysed coupling in the case of *N*-aryl sulfoximines **145** and **146** (Scheme 118).[102]



Scheme 118

All large scale reactions to produce sulfoximine **142** from DMSO involved very toxic and potentially explosive reagents and drastic conditions (NaN_3/H_2SO_4, MSH), thus the reduction of the commercially available *N*-tosyl sulfoximine **137** was selected as the safest route. Moreover, several methods involving cheap reagents (Chloramine-T or tosyl azide)[21, 22] were available to synthesise **137** from DMSO (Scheme 119).

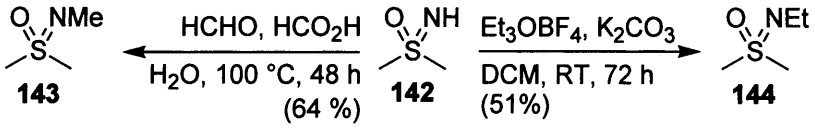


Scheme 119

The cleavage of the tosyl group of **137** was effected by sodium anthracenide[25] solution in DME at 0 °C, followed by an acidic work-up but isolation of the *NH*-sulfoximine **142** proved to be rather complicated because of its solubility in the aqueous phase. After acidification of the reaction mixture with 3M hydrochloric acid to solubilise **142** in the aqueous phase, impurities (anthracene and tosyl by-products) were extracted with DCM.

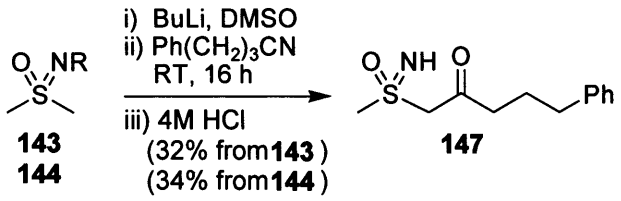
The aqueous phase was neutralised, the water was removed and the dry residue triturated with DCM to finally isolate **142** as a pale yellow solid in 77% yield.

To achieve the alkylation of the nitrogen atom, the most common method utilises a strong electrophile, such as trimethyloxonium tetrafluoroborate or methyl iodide;[161, 162] another procedure using formaldehyde/formic acid, known as the Eschweiler-Clark alkylation to synthesise tertiary *N*-methyl amines, could also lead to the targeted *N*-methyl sulfoximine **143**.[86] Both reactions with trimethyloxonium tetrafluoroborate and methyl iodide gave a mixture of the desired product along with unreacted starting material. A laborious work-up due to the high solubility of both starting material and product in the aqueous phase resulted in considerable loss of material. Finally, following Eschweiler-Clark conditions, *N*-methyl sulfoximine **143** was synthesised in 64% yield, however this reaction needs to be run on at least 1 g to obtain satisfactory yields.
N-Ethyl sulfoximine **144** was obtained as a yellow oil in 51% yield by reaction of **142** with triethyloxonium tetrafluoroborate in the presence of potassium carbonate in DCM (Scheme 120).



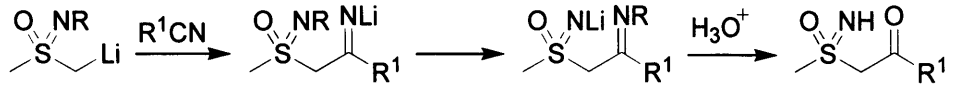
Scheme 120

Compounds **143** and **144** were then subjected to the condensation reaction with 4-phenylbutyronitrile under the same conditions as those used on the *N*-tosyl derivative (Scheme 121).



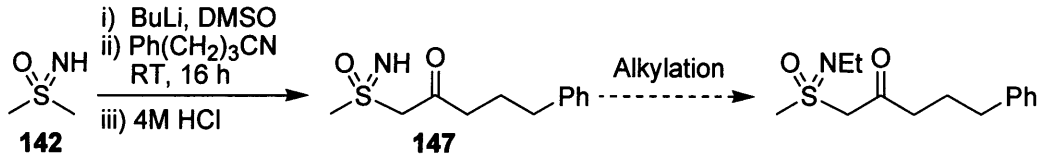
Scheme 121

Conversion of the *N*-alkylsulfoximines **143** and **144** to the corresponding β-keto derivatives was accompanied, unexpectedly, by loss of the *N*-alkyl substituent to give **147** in both cases. The reason for this dealkylation is unclear, but it is possible that, following reaction of the sulfoximine anion with the nitrile, the alkyl group is transferred to the imine nitrogen; this is then lost as an alkylamine upon hydrolysis (Scheme 122).



Scheme 122

We tried to overcome this problematic migration by changing the sequence of steps (Scheme 123).

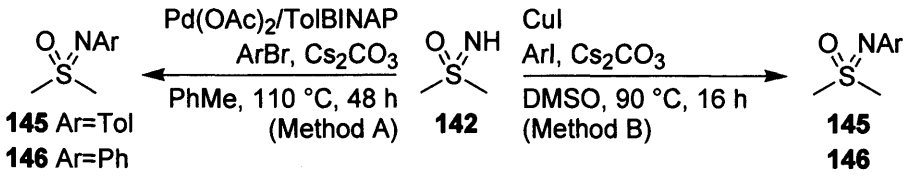


Scheme 123

The major problem in the first step is the difficulty of controlling the reaction site; along with compound **147** several undesired products were detected. The isolation of β-ketosulfoximine **147** proved to be rather tricky and even after several purifications by column chromatography on silica the desired product was still impure but was used as such. Compound **147**, obtained either from rearrangement of the imine intermediate

(Scheme 122) or from direct condensation of the *NH*-sulfoximine **142** on 4-phenylbutyronitrile (Scheme 123), was subjected to an alkylation reaction using triethyloxonium tetrafluoroborate (Scheme 120). Due partly to the contamination of the starting material and the several possible alkylation sites leading to various products, the reaction could not be exploited even after attempts made to purify the mixture.

We focused then on the synthesis of *N*-aryl derivatives, thinking that an aryl group would not migrate during the condensation reaction with a nitrile and thus the loss of the substituent would be avoided. The synthesis of such compounds was based on Bolm's work published in 2000,[102] a palladium-catalysed cross-coupling between an aryl bromide and a sulfoximine (method A), which is reported to afford the corresponding *N*-aryl sulfoximines in high yields. Another method to synthesise *N*-aryl sulfoximines was tested (method B),[113, 118] a copper-mediated coupling in DMSO (Scheme 124). Two compounds were targeted, namely *N*-tolyl- and *N*-phenyl- *S,S*-dimethylsulfoximines **145** and **146** (Table 20). The latter compound has been described previously in the literature, and was used as a reference to test the procedure.



Scheme 124

Table 20: *N*-Arylation

Entry	Conditions	Yield
a	Method A: $Pd(OAc)_2$ (0.05 eq.), TolBINAP (0.075 eq.) TolBr (1.0 eq.), sulfoximine (1.25 eq.) PhMe, 110 °C, 48 h	5%
b	Method A, reaction time: 72 h	8%
c	Method A, halide: PhBr	15%
d	Derived from Method A $Pd(OAc)_2$ (0.05 eq.), TolBINAP (0.075 eq.) TolBr (1.25 eq.), sulfoximine (1.0 eq.) PhMe, 110 °C, 96 h	15%
e	Derived from Method A $Pd(OAc)_2$ (0.2 eq.), BINAP (0.1 eq.) TolBr (1.25 eq.), sulfoximine (1.0 eq.) PhMe, 110 °C, 48 h	No clean product isolated
f	Method B: CuI (1.0 eq.), PhI (2.0 eq.) sulfoximine (1.0 eq.) DMSO, 90 °C, 12 h	no reaction

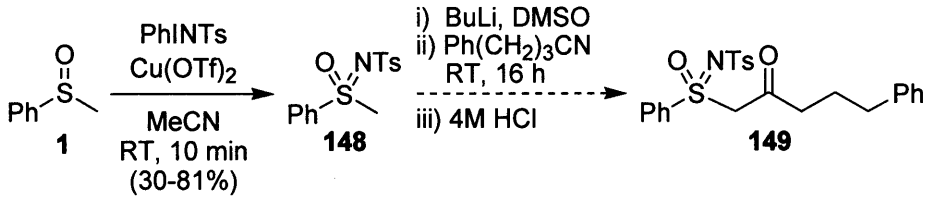
The standard procedure of method A (Entry a) afforded *N*-tolyl sulfoximine in very low yield (5%), and increasing the reaction time did not have any significant effect (8% yield,

Entry b). Using bromobenzene resulted in the formation of *N*-phenyl sulfoximine in slightly better yield (15%, Entry c) and the same yield was obtained when an excess of bromotoluene and a longer reaction time was used (Entry d). To change for another catalytic system (Entry e) did not improve the yield of this coupling and the starting material was also inert to the reaction conditions of method B (Entry f). In conclusion, arylation of **142** to afford *N*-tolylsulfoximine **145** or *N*-phenylsulfoximine **146** proceeded in low yield and the copper-mediated cross coupling methods[113, 118] we tried to apply were not successful at all.

To summarize, *N*-alkyl sulfoximines underwent an unexpected migration of the alkyl group during condensation with a nitrile and the access to the corresponding β-ketosulfoximines by another route was not successful, so we were not able to investigate diazo transfer for this series of sulfoximines. To avoid such rearrangement, we focused on the synthesis of *N*-aryl sulfoximines and expected to study the behaviour of the corresponding β-ketosulfoximines during diazo transfer. However, despite literature precedent and extensive experimentation the very low yield for the *N*-arylation led the investigation to a dead end. Having failed to obtain any information about the decomposition pathway by changing the substituent on the nitrogen, we aimed then to modify the substituent attached to the sulfur atom with the hope to synthesise a new series of sulfoximines as starting materials for the investigation on diazo transfer reaction.

2.1.3. Changing the substituent attached to the sulfur atom

We decided to examine the effect of the substituent attached to the sulfur atom and thus we chose to synthesise *N*-tosyl methylphenylsulfoximine **149** from commercially available methylphenyl sulfoxide **1** and to carry out the sequence leading to the β-ketosulfoximine **149**, by analogy with the sulfoximine **139** used at the commencement of the project (Scheme 125).



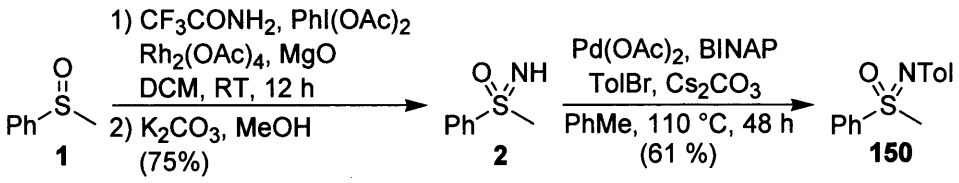
Scheme 125

Sulfoxide **1** was treated with the iminoiodinane species PhINTs[45] in the presence of a catalytic amount of copper(II) triflate in acetonitrile, following a 2004 procedure from Malacria *et al.*[44] affording the corresponding sulfoximine **148** in 81% yield., although this yield dropped sharply when the scale of the reaction exceeded 300 mg scale.

The condensation of sulfoximine **148** with 4-phenylbutyronitrile in the standard conditions described in the previous sections, failed after several trials. Deprotonation of **148** under a range of conditions followed by quenching with deuterated water or methanol led only to low (and non-reproducible) levels of deuterium incorporation. In the best cases, 20% deuterium incorporation was observed after reaction of **148** with 1.3 eq. of butyl lithium in dry THF at -40 °C (concentration of the reaction mixture: 0.3 M). Due to the poor deprotonation rate, the loss of material was too significant to obtain sufficient amount of β-ketosulfoximine **149** when Johnson's method[159] was used, only traces of **149** were identified in the crude reaction mixture.

Since the hindrance of the deprotonation site generated by both the phenyl and the tosyl groups was deleterious to the preparation of β-ketosulfoximines, we decided to vary the substituent on the nitrogen atom for this series and to investigate *N*-aryl derivatives (Scheme 126).

Following a procedure by Bolm *et al.*,[46] reaction of sulfoxide **1** with the hypervalent iodine species formed *in situ* from trifluoroacetamide and iodobenzene diacetate in the presence of rhodium acetate, followed by deprotection of the non-isolated intermediate, led to the formation of the *NH*-sulfoximine **2** as a yellow oil in 75% yield.



Scheme 126

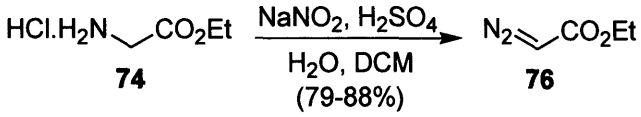
Derivatisation of **2** by palladium-catalysed cross-coupling with bromotoluene afforded *N*-tolyl sulfoximine **150** in 61% yield.[102] *N*-Tolyl derivative **150** was subjected to the condensation reaction with 4-phenylbutyronitrile, in the same conditions as described previously, but no desired product could clearly be isolated apart from unreacted starting material. Analysis of the proton NMR spectrum of the crude reaction mixture showed traces of the desired β-ketosulfoximine; purification by column chromatography on silica did not lead to enough material for full characterisation.

In conclusion, the planned investigation of the diazo transfer reaction on various β-ketosulfoximines could not be carried out due to unrelated problems in the steps preceding the diazo transfer. The inability to obtain sufficient quantities of *N*-aryl sulfoximines, the unexpected loss of the alkyl group attached to the nitrogen in the sulfoximine moiety during the condensation with a nitrile, and the difficult deprotonation of *S*-methyl-*S*-phenyl sulfoximines in the analogous step, closed all the routes to β-ketosulfoximines as well as any investigation on diazo transfer reactions. At this point, we chose to investigate the synthesis of acyclic α-diazosulfoximines by other routes.

2.2. Towards acyclic α-diazosulfoximines by an alternative route

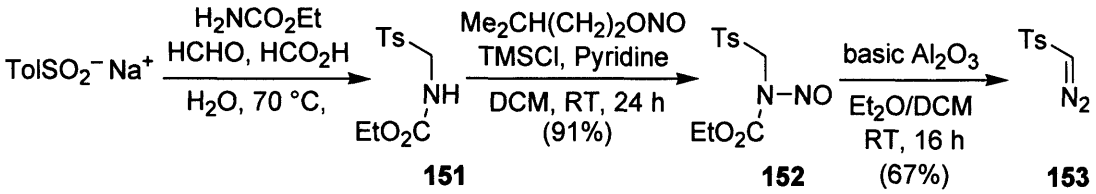
Numerous diazo compounds have been prepared by reaction of primary amines or secondary carbamates with nitrosating reagents. For example, the *Organic Syntheses* procedure from 1977 for the preparation of ethyl diazoacetate **76** involves treatment of the salt of ethyl glycinate **74** with sodium nitrite in acidic solution (Scheme 127),[163] and a recent procedure for the preparation of tosyldiazomethane **153** consists of conversion of

carbamate **151** to its *N*-nitroso derivative **152** using a mixture of trimethylsilyl chloride and isoamylnitrite, and subsequent reaction with basic alumina to generate diazo compound **153** (Scheme 128).[164]



74 76

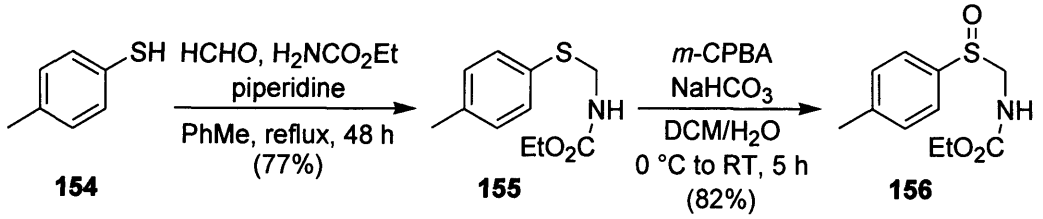
Scheme 127



151 **152** **153**

Scheme 128

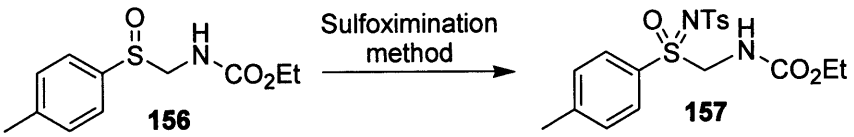
We chose to investigate the latter method for the synthesis of a diazosulfoximine according to the sequence depicted above; the first target was carbamate **156,** synthesised in two steps from 4-methylbenzenethiol **154** (Scheme 129).



154 **155** **156**

Scheme 129

Three-component condensation of 4-methylbenzenethiol **154** with formaldehyde and ethyl carbamate in refluxing toluene afforded secondary carbamate **155** in 77% yield; oxidation of the sulfur with *m*-CPBA was successful to give **156** in 82% yield.



Scheme 130

However, treatment of sulfoxide **156** with iminoiodinane PhINTs and either copper(II) triflate or copper(I) triflate catalysts, led within two minutes to extensive decomposition, and none of the expected sulfoximine **157** (Scheme 130). Other imination reagents (Chloramine-T) or other systems such as phosphorus pentoxide with tosylamide in the presence of triethylamine ($P_2O_5/Et_3N/TsNH_2$) on either sulfide **155** or sulfoxide **156** were equally unsuccessful.

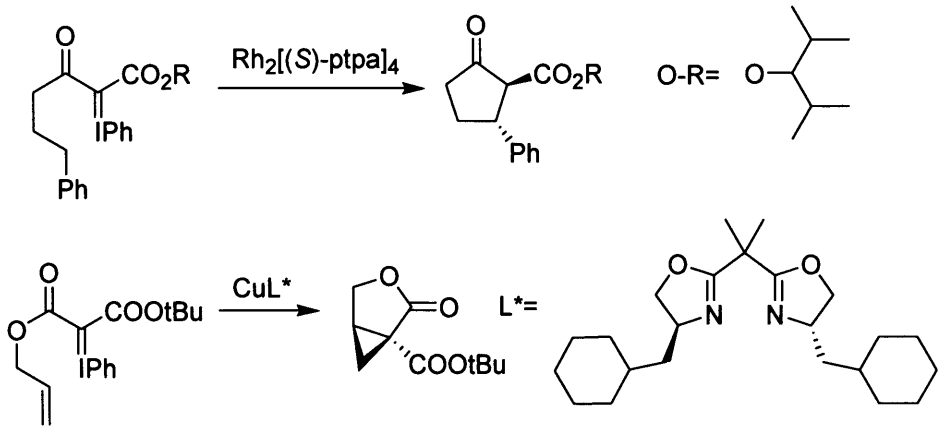
Having failed to generate an acyclic α-diazo-β-ketosulfoximine, and with the suspicion that such species may be somewhat unstable, we decided firstly to explore the possibility of generating metal carbenes from sulfoximines without the intermediacy of a diazo compound.

2.3. Non-diazo routes to sulfoximino-carbenes

During the last decade of the 20th century, the interest in iodine compounds has experienced an explosive development mainly due to the very useful oxidizing properties of polyvalent organic iodine reagents combined with their benign environmental character and commercial availability. Several areas of organic polyvalent iodine chemistry have recently attracted active interest and research; among them the use of iodonium ylides as convenient precursors to the respective carbene intermediates in transition-metal-catalyzed reactions.

These species are readily available through the reaction of active methylene compounds with hypervalent iodine reagents, and react with rhodium and copper catalysts to generate metal carbenes[165, 166] and subsequent insertion and/or cyclopropanation. As one example of this research area, the scope and mechanism of the metal-catalysed carbenoid

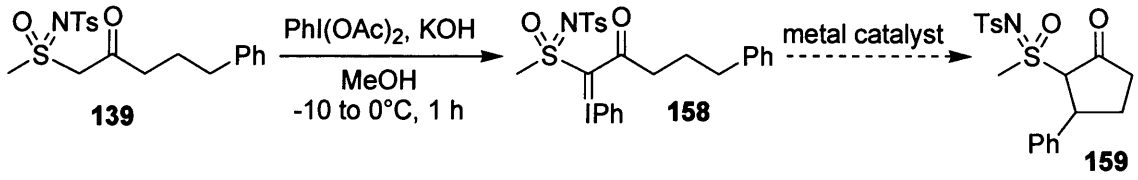
decomposition of iodonium ylides with regard to their application in asymmetric carbenoid reactions were investigated by Müller and coworkers[167] (Scheme 131).



Scheme 131

2.3.2. Attempted isolation of iodonium ylides

Initially we tried to convert β-ketosulfoximine **139** to a phenyliodonium ylide **158** by treatment with iodobenzene diacetate in basic methanolic solution (Scheme 132).[168]



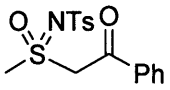
Scheme 132

A crude reaction mixture was obtained in which the characteristic AB system of the starting material had disappeared from the ^{1}H NMR spectrum, suggesting successful formation of iodonium ylide **158** had occurred; when iodobenzene diacetate was used in DCM, either in the presence of triethylamine or not, the AB system also disappeared. However, upon attempted purification of the reaction mixture by chromatography (on

silica or Florisil®), decomposition occurred and full characterisation of **158** proved impossible.

Attempts were therefore made to utilise the iodonium ylide **158** without purification; it was hoped that reaction of the crude ylide with a metal catalyst would effect intramolecular C-H insertion to give cyclopentanone **159**. In practice, treatment of the mixture of compounds from the hypervalent iodine reaction with a variety of metal catalysts ($Rh_2(OAc)_4$, $Cu(acac)_2$, $Cu(hfacac)_2$) did not give any isolable products.

The corresponding experiments were carried out using β-ketosulfoximine **160** (Figure 25), first we tried to isolate the corresponding iodonium ylide; that failing we attempted to use the ylide without purification, in metal-catalysed cyclopropanation reactions with stilbene and styrene, but these were unsuccessful.

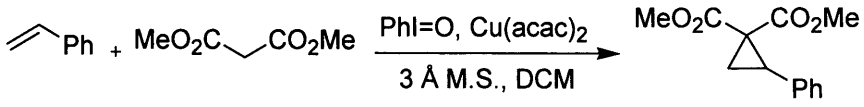


160

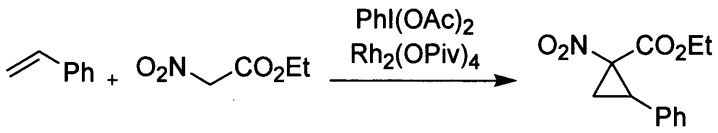
Figure 25

2.3.2. Attempted formation of metal carbenes without precursor isolation

The use of iodonium ylides as unisolated intermediates in the generation of metal carbenes is a fairly recent development. Such carbenes have been generated in this way from β-dicarbonyl compounds[169, 170] (Scheme 133) and from α-nitroesters (Scheme 134).[171, 172] By generation of these carbenes in the presence of an alkene such as styrene, cyclopropanes may be formed directly.

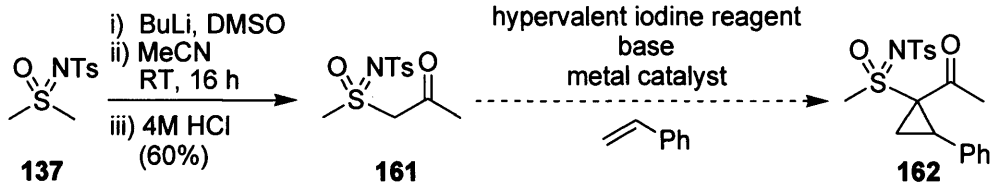


Scheme 133



Scheme 134

Our attempts to carry out this chemistry in the context of sulfoximine chemistry are shown in Scheme 135; β-ketosulfoximine **161** was prepared in the same manner as **139**, by condensation of sulfoximine **137** with acetonitrile. Reactions of **161** with styrene in the presence of various hypervalent iodine reagents, bases and catalysts are summarised in Table 21.



Scheme 135

Table 21

Entry	Procedure	Result
a	$Rh_2(OAc)_4$ (5 mol%), styrene (10 eq.), PhI=O (1.4 eq.) MgO (2.3 eq.), M.S. 4Å, DCM, 10 °C to RT, 40 h	no reaction
b	$Rh_2(OAc)_4$ (5 mol%), styrene (10 eq.), $PhI(OAc)_2$ (1.4 eq.) Na_2CO_3 (2.3 eq.), M.S. 4Å, DCM, 10 °C to RT, 40 h	no reaction
c	CuCl (2 mol%), $AgSbF_6$ (2.4 mol%), styrene (5 eq.) PhI=O (1.1 eq.), Na_2CO_3 (2.3 eq.), M.S. 4Å, PhH, RT, 3 h	no reaction
d	CuCl (2 mol%), $AgSbF_6$ (2.4 mol%), styrene (5 eq.) $PhI(OAc)_2$ (1.1 eq.), Na_2CO_3 (2.3 eq.) M.S. 4Å, PhH, RT, 40 h	no reaction
e	CuCl (2 mol%), $AgSbF_6$ (2.4 mol%), styrene (5 eq.) PhI=O (1.1 eq.), Na_2CO_3 (2.3 eq.), M.S. 4Å, DCM, RT, 40 h	no reaction
f	CuCl (2 mol%), $AgSbF_6$ (2.4 mol%), styrene (5 eq.) PhI=O (1.1 eq.), KOH (2.3 eq.), M.S. 4Å, DCM, RT, 40 h	no reaction

Literature conditions for cyclopropanation with dimethylmalonate (Entry a) taken from a 2004 publication from Müller,[170] did not show any reaction and only starting material was recovered; changing the hypervalent iodine source for iodobenzene diacetate had no effect (Entry b). The second procedure for cyclopropanation we tried was from a 2005 paper from Charette[172] based on copper catalysis (Entry c); in this case again no reaction

was detected. Again, changing the iodine source to iodobenzene diacetate (Entry d), the solvent to DCM (Entry e) or the base to potassium hydroxide (Entry f) did not initiate the reaction and in every case, the starting material was recovered.

In a further attempt to explore the utility of such conditions for the synthesis of sulfur-substituted cyclopropanes, a methyl sulfone and a phenyl sulfone (Figure 26) corresponding to the sulfoximine **161** were also subjected to the same reaction conditions according to the procedure of Müller.

Figure 26

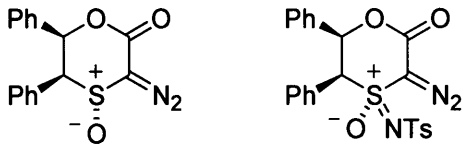
No cyclopropanation was observed with either of these reagents, although cyclopropanation of styrene with dimethyl malonate *was* successful, as reported in the literature.

At this stage, having tried several methods we could not synthesise an acyclic α-diazo-β-ketosulfoximine, and the investigation to obtain metal carbenes from iodonium ylides that could be isolated or generated *in situ* led only to results showing decomposition or no reaction. We decided to turn our research efforts in other directions to circumvent the instability of acyclic β-ketosulfoximines and given Maguire's observations on the greater stability of cyclic diazosulfoxides compared to their acyclic analogues, we aimed to investigate the possibility of synthesising a cyclic α-diazo-β-ketosulfoximine.

2.4. Routes to cyclic α-diazosulfoximines

2.4.1. Sulfoximines derived from 5,6-diphenyl-1,4-oxathiane-2-one

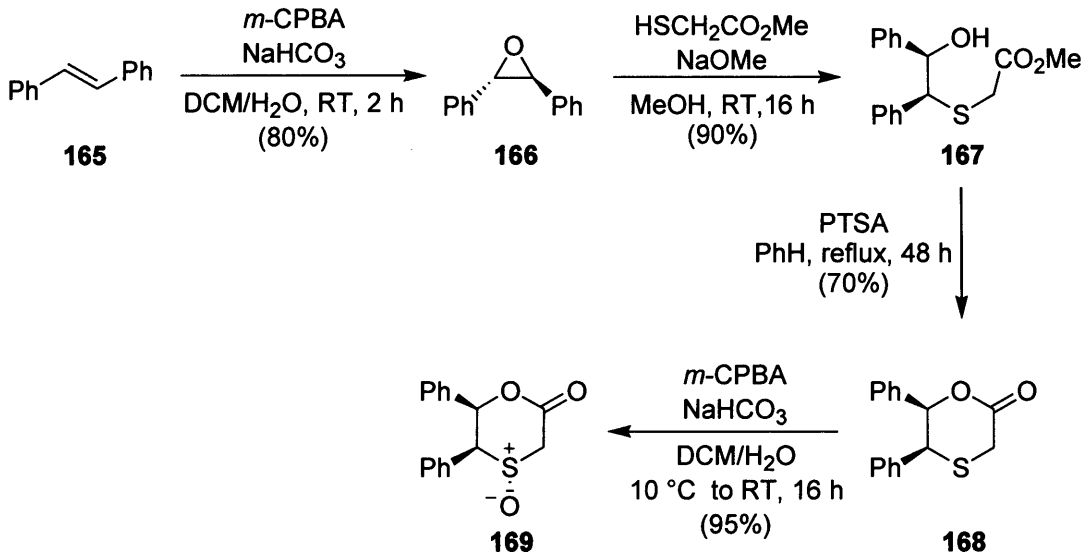
The identification of sulfonamide by-products from *p*-ABSA and *p*-CBSA in the attempted diazo transfer reactions, led us to think that the instability of the product, rather than failure of the diazo transfer step, was the reason we were unable to isolate acyclic α-diazo-β-ketosulfoximines. The closest report to our project was a 1998 paper by Maguire, outlining the isolation of cyclic diazosulfoxides.[9] In this publication, cyclic α-diazo-β-ketosulfoxides were shown to be more stable than their linear analogues and a route to diazosulfoxide **163** was developed. We decided to take this as a starting point, and aimed to prepare the corresponding *N*-tosyl diazosulfoximine **164** (Figure 27).



163 **164**

Figure 27

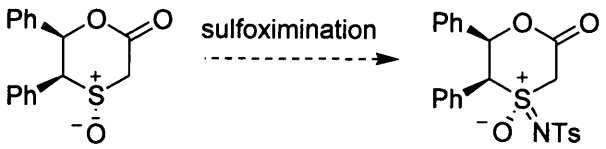
The route to sulfoxide **163** is depicted in Scheme 136 according a route published in 1992 by García Ruano,[173] only the lactonisation step has been modified.



Scheme 136

Stilbene **165** was treated with *m*-CPBA in a biphasic system DCM/$NaHCO_3$ (saturated aqueous solution) to afford epoxide **166** in 80% yield.[174] The resulting epoxide was opened with methyl thioglycolate in methanol to obtain hydroxyester **167** in 90% yield, which was subjected to acid-catalysed lactonisation[175] to yield lactone **168** as white needles in 70% yield. Oxidation of **168** to a sulfoxide was carried out with *m*-CPBA,[176] in the same biphasic system used for the epoxidation step, affording sulfoxide **169** in 95% yield as a single isomer, as described by Maguire.

We then investigated methods to convert sulfoxide **169** to the corresponding sulfoximine **170** (Scheme 137, Table 22)



169 **170**

Scheme 137

Table 22

Entry	Reaction conditions[1]	Result
a	PhINTs (1.1 eq.), $Cu(OTf)_2$ (10%), RT	Decomposition
b	PhINTs (1.1 eq.), $Cu(OTf)_2$ (3 to 10%)	Decomposition
c	PhINTs (1.1 eq.), $Cu(acac)_2$ (10%), RT and 2 °C	Decomposition
d	PhINTs (1 to 1.5 eq.), $Cu(acac)_2$ (5%)	Decomposition
e	PhINTs (1 to 1.5 eq.), $Cu(OAc)_2$ (5 and 10%)	Decomposition
f	PhINTs (1 eq.), Cu(OTf)(benzene) complex (5 to 15%)	Decomposition
g	Chloramine-T (1.2 eq.), MeCN or DCM, RT	No reaction
h	MSH (1 eq.), MeCN or DCM/$NaHCO_3$ (1:1),[2] RT	Partial reaction

[1] Reactions were set up in acetonitrile at room temperature except when otherwise mentioned.

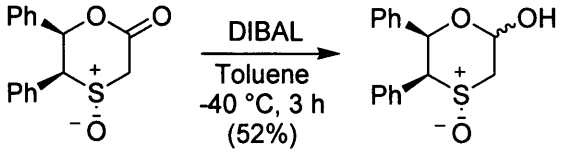
[2] Saturated bicarbonate aqueous solution.

The first sulfoximination reaction conditions we tried were those described by Malacria *et al.*[44] (Entry a). While these led to the disappearance of starting material within a short time, decomposition also occurred and no products could be identified in the crude mixture. Thinking that our sulfoxide was perhaps also sensitive to the triflic acid generated during the reaction, we subjected the substrate to other copper catalysts which contained to more basic ligands (Entries b-f). We limited the choice to copper catalysts which successfully catalysed sulfoximination reactions during the screening of catalysts done in

Malacria's study. However, in all cases, NMR analysis showed that the reaction led to decomposition of the starting material.
We also tried methods without metal catalysis and in this field, amination can be achieved with Chloramine-T (Entry g), but in our case no reaction was detected and only starting material was recovered.
When MSH was used (Entry h), the sulfoxide partly disappeared, ^{1}H NMR spectrum of the crude mixture showed that a relatively clean reaction had taken place, but no product could be identified.

These results showing either decomposition or no reaction at all came perhaps unsurprisingly, as a systematic study of sulfoximination methods by Tye *et al.* had shown that an acyclic β-ketosulfoxide, methyl (phenylsulfinyl)acetate, was inert to all the conditions tried.[40] These authors assigned this lack of reactivity to the electron-withdrawing effect of the carbonyl group, making the lone pair on the sulfur less nucleophilic.
In our case the starting material decomposed within a short time perhaps due to a coordination of the copper(II) to the lactone carbonyl thus inducing the opening of the cycle.

To remove any interference from the lactone carbonyl, **169** was reduced to the lactol **171** using DIBAL in toluene (Scheme 138).

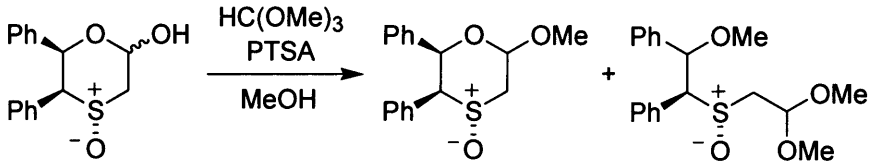


169 **171**

Scheme 138

The reduction reaction of the carbonyl proved troublesome, yielding the **171** in rather low yield (52%) after several trials, and examination of the crude mixture revealed that several open-chain products had been formed, perhaps due to the long reaction time

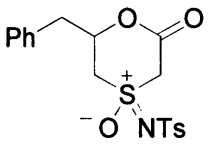
necessary to complete the reaction. Protection of the lactol **171** by reaction with trimethyl orthoformate in the presence of *p*-toluenesulfonic acid (Scheme 139) afforded acetal **172** in 14% yield, however it was complicated by the formation of **173** as the major product (15% yield) which was presumed to arise due to the ready formation of a benzylic cation.



171 **172** **173**

Scheme 139

To overcome these problems we decided to target a new cyclic β-ketosulfoximine, substrate **174**, in which no benzylic C-O bond was present (Figure 28).



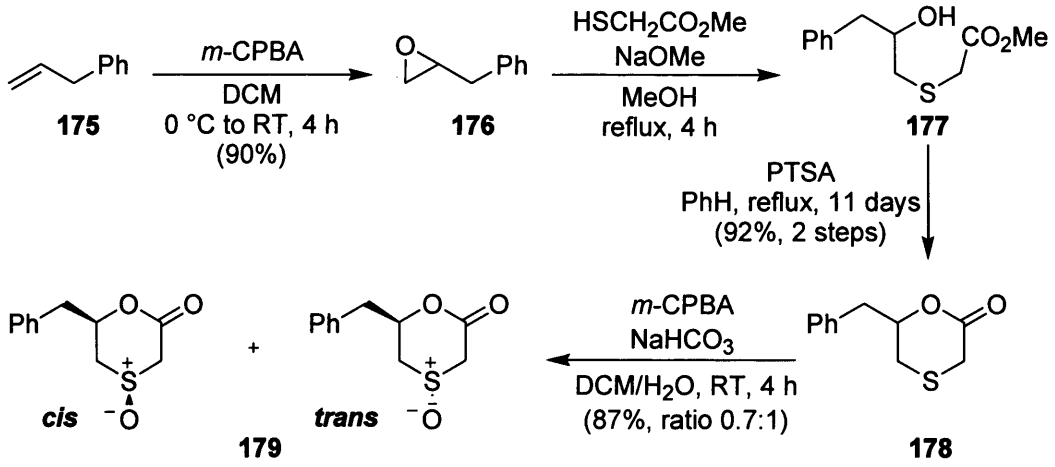
174

Figure 28

2.4.2. Sulfoximines derived from 2-benzyl-1,4-oxathiane-2-one

We decided to synthesise sulfoxide **179**, following an analogous route to that described previously. The two major advantages of this new target over the first one were the suppression of the possible formation of a benzylic cation and a less hindered sulfur atom.

Starting from allylbenzene, the synthesis of **179** proceeded uneventfully following the same or slightly modified sequence of steps (Scheme 140).

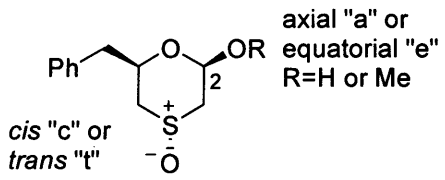


Scheme 140

Allylbenzene **175** was converted to benzyloxirane **176** with *m*-CPBA in 90% yield and **176** was then opened with methyl thioglycolate. The resulting crude hydroxyester **177** only contained the excess of thioglycolate thus was not isolated and was subjected to cyclisation, yielding lactone **178** in 92% yield over two steps. In the case of hydroxyester **177**, the lactonisation step took much longer than that for the first hydroxyester **167**, but the yield increased significantly, from 70% up to 96%. Lactone **178** was then oxidised with *m*-CPBA in a biphasic system affording sulfoxide **179**; in contrast to the complete stereocontrol observed in the oxidation step of the first lactone **168**, oxidation of **178** gave a mixture of diastereomeric sulfoxides **179** (0.7:1 *cis:trans* ratio) in 87% combined yield, which were with difficulty, separable. The relative stereochemistry was assigned at a subsequent stage - *vide infra*.

From this point we carried out the remainder of the synthesis towards sulfoximines with the two series that arose from the oxidation step, investigating reaction steps in parallel. This way we could obtain relevant information about the influence of the relative stereochemistry between the sulfoxide and the benzylic group during the sulfoximination reaction.

The compounds synthesised in this section are labelled according to their stereochemistry (Figure 29):



R=H: *t*-**180e**

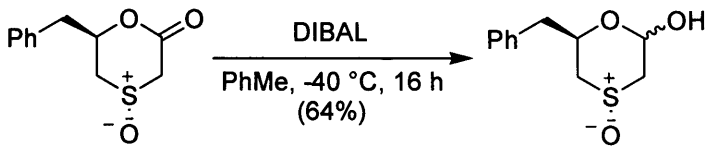
Figure 29

- compounds are referred to as " c" and " t" depending on the relative stereochemistry (cis or trans) between the sulfoxide and the benzyl group;

- the stereochemistry of the chiral centre at C2 is indicated as either axial "a" (alkoxy trans to the benzyl group) or equatorial "e" (alkoxy cis to the benzyl group);

- if the compound label does not specify the stereochemistry, it refers to a mixture of diastereomers.

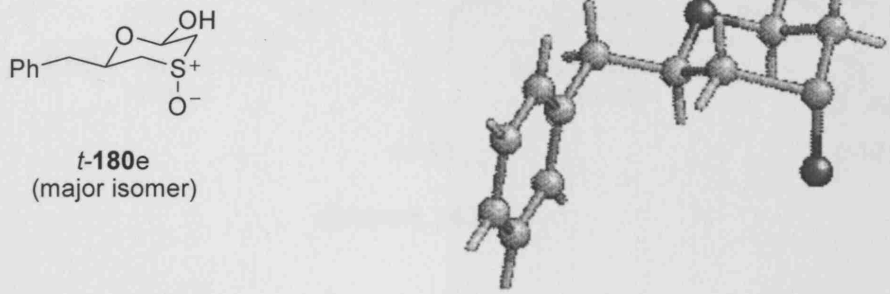
DIBAL reduction of isomer *t*-**179** gave the corresponding lactol *t*-**180**, which existed as a 0.7:1 ratio of diastereomers in deuterated chloroform solution, in 64% yield (Scheme 141); ^{1}H NMR analysis of the crude reaction mixture did not show formation of open-form products. In some cases lactone **168**, obtained by reduction of the sulfoxide rather than the lactone, was identified as the major by-product of this step.



t-**179** *t*-**180**

Scheme 141

A controlled recrystallisation by slow evaporation of ethyl acetate produced a single crystal of the major isomer which permitted assignment of the relative stereochemistry of the major isomer of *t*-**180e** by single crystal X-ray diffraction (Figure 30).

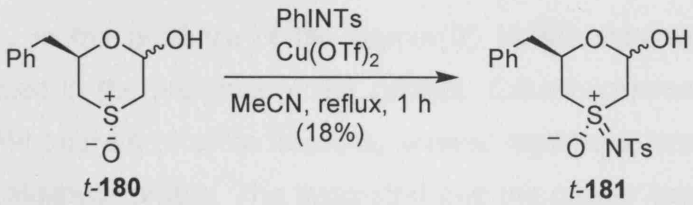


t-**180**e
(major isomer)

Figure 30

Since no open-form products had been identified showing that this new cyclic substrate was more stable than the previous one, we decided to try sulfoximination directly on *t*-**180**; if it was successful we could avoid a protection-deprotection sequence.

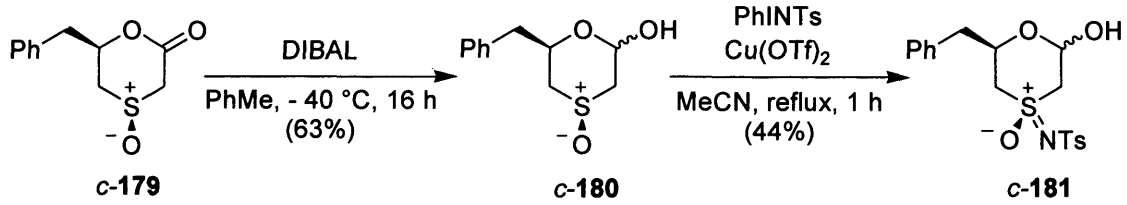
Imination of *t*-**180** with iminoiodinane PhINTs in the presence of copper(II) triflate gave the corresponding sulfoximine *t*-**181**, which exists as a 0.4:1 mixture of diastereomers in deuterated chloroform solution, in 18% yield (Scheme 142). Various changes in the reaction conditions have been made to improve the yield, but despite extensive work to optimise this step, sulfoximination of *t*-**180** was uniformly reproducible with 17-18% yield only.



t-**180** *t*-**181**

Scheme 142

The *cis* series was more difficult to investigate, as reduction with DIBAL and subsequent sulfoximination were not as reproducible as those in the *trans* series but yields were in general better (Scheme 143). DIBAL reduction of *c*-**179** afforded lactol *c*-**180** in 63% yield with a 0.3:1 ratio of diastereomers in deuterated chloroform solution; the corresponding sulfoximine *c*-**181** was obtained in 44% yield.

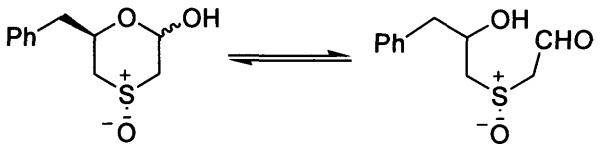


c-**179** *c*-**180** *c*-**181**

Scheme 143

The reproducibility of the sulfoximination reaction for the *trans* series, despite the low yield, the fact that no other product could be identified in the crude mixture and also that all starting material had disappeared, suggested that nitrene transfer had taken place but the lactol had partly decomposed.

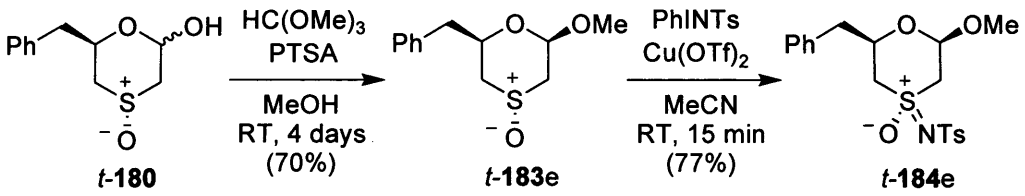
In fact, in the reaction conditions the lactol *t*-**180** is in equilibrium with an open-form hydroxy-aldehyde **182** which exhibits a β-ketosulfoxide pattern (Scheme 144), known from previous experiments to be inert or to destabilise the whole structure.



t-**180** **182**

Scheme 144

Studies of stability in the presence of the copper(II) triflate showed that the starting material decomposed in the presence of the catalyst. Column chromatography on silica followed by ^{1}H NMR analysis of some fractions, showed significant peaks in the range of chemical shift for aldehyde proton. This suggested that the copper catalyst induced ring-opening of the starting material. In the reaction conditions, the equilibrium between both compounds seems to be in a 4:1 ratio in favour of the open-form, which could explain the low (18%) but reproducible yield, thus the yield should increase if the structure is locked as a cycle by protection of the lactol as an ether (Scheme 145).



Scheme 145

Reaction of *t*-**180** with trimethyl orthoformate[177] afforded the corresponding acetal *t*-**183**e in 70% yield as a single isomer with the methoxy group in the equatorial position (Figure 31). Subsequent sulfoximination of the acetal led to the sulfoximine *t*-**184**e in 77% yield.

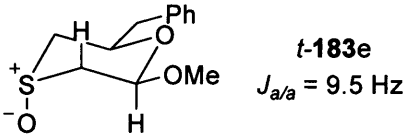
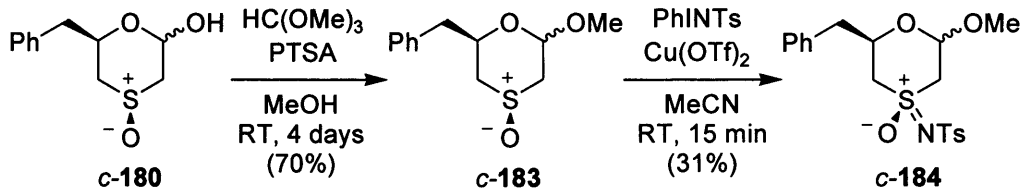


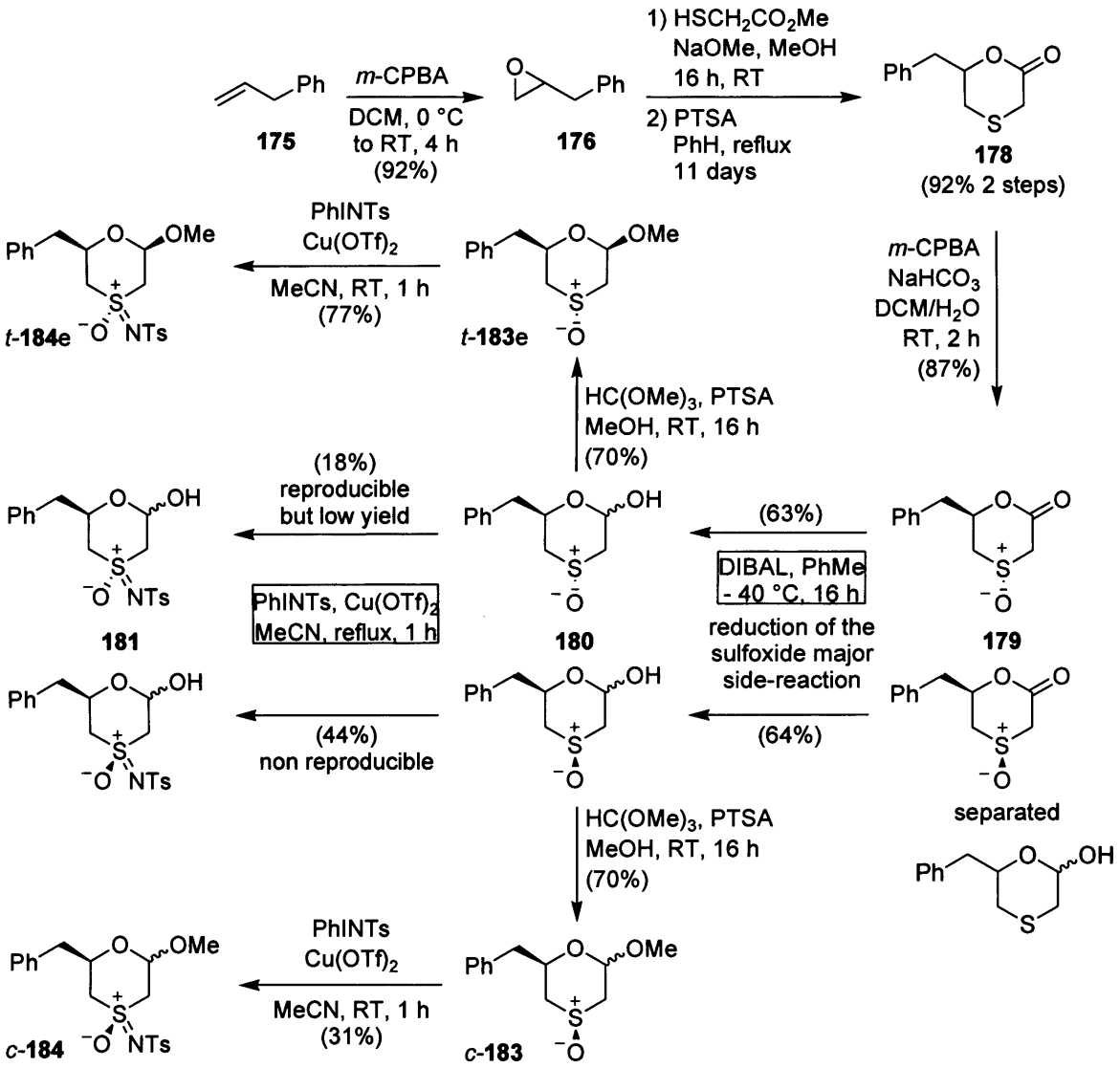
Figure 31

In the *cis* series, protection of the lactol *c*-**180** in the same reaction conditions yielded the corresponding acetal *c*-**183** in 70% yield as a mixture of diastereomers, however the ratio of products and the identity of the major isomer varied from reaction to reaction. Sulfoximine *c*-**184** was obtained in 31% yield as a mixture of diastereomers, with the same reaction conditions as for the *trans* series (Scheme 146).



Scheme 146

To summarise, up to now we have been able to achieve sulfoximination reaction for the cyclic substrates **180** and **183** in each series, following a sequence of steps summarised in Scheme 147.



Scheme 147

Oxidation of allyl benzene **175** proceeded in high yield (92%), the opening of the resulting epoxide **176** with thioglycolate followed by cyclisation of the crude hydroxyester, afforded lactone **178** in 92% yield over two steps; lactone **178** was synthesised smoothly in high yield.

Oxidation of the sulfur led to two isomers of **179** with very close polarity on silica, which made their separation tricky; on large scale reactions, several chromatographies on silica were necessary to isolate one from the other.

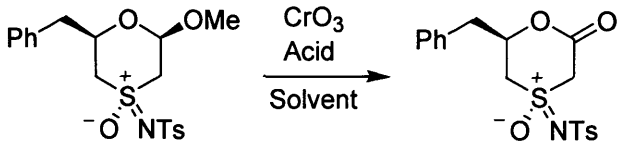
The yield of the reduction of lactone **179** to their corresponding lactol **180** was satisfactory, however ^{1}H NMR analysis of the crude mixture and some fractions isolated

from chromatography revealed that the formation of lactone **178** by reduction of the sulfoxide, was a major side-reaction of this step.

Protection of lactol **180** as ethers was uneventful and the yield of the resulting acetals **183** was acceptable (70%). Sulfoximination reaction of *t*-**183** proceeded well with high yield (77%) and purification by column chromatography has been easy, in the cis series the yield of the sulfoximination was rather low (31%) and the purification was messy.

In an overall picture, reactions in the *cis* series have been far less reproducible than those in the *trans* series and moreover, side-reactions and difficult separations led to considerable loss of material and a laborious investigation.

Despite the difficulties encountered in each series, we decided to investigate first conversion of sulfoximine **184** directly to the corresponding lactone via Jones oxidation (Table 23). However, because of the low reproducibility of the reactions in the *cis* series, oxidations were mostly tried with *t*-**184**e (Scheme 148).



t-**184**e *t*-**174**

Scheme 148

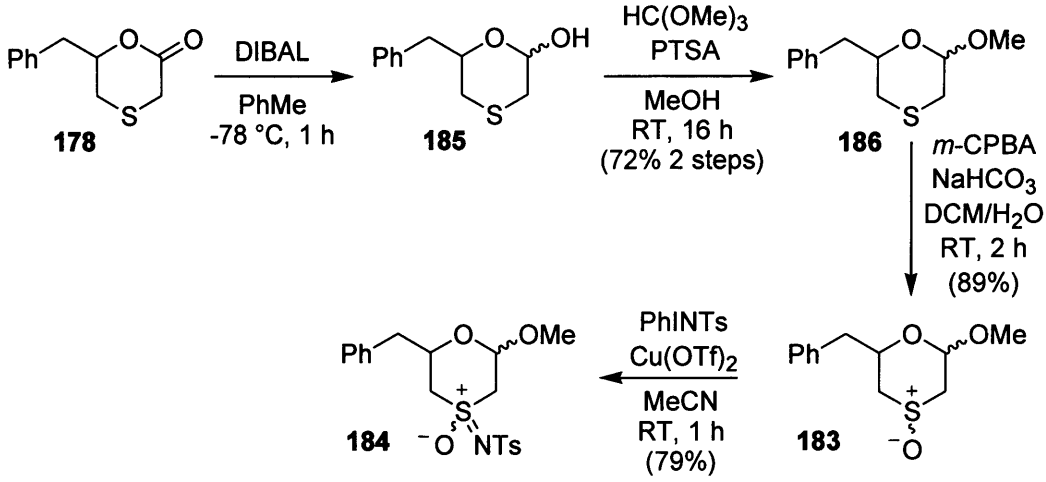
Table 23

Entry	Reaction Conditions	Results
a	CrO_3, H_2SO_4, Acetone/H_2O 3:1, RT, 22 h	No reaction
b	CrO_3, H_2SO_4, DCM/H_2O 1:1, RT, 16 h	No reaction
c	CrO_3, H_2SO_4, DCM/H_2O 2:1, 50 °C, 20 h	No reaction
d	CrO_3, H_2SO_4, DCE/H_2O 1:1, 80°C, 16 h	No reaction
e	CrO_3, AcOH, DCM/H_2O 10:1, RT, 16 h[178] then 45 °C, 60 h.[179]	No reaction
f	CrO_3, AcOH, H_2O, 80 °C, 20 h	No reaction

Standard conditions for Jones oxidation[180, 181] (Entry a) were not suitable due to the poor solubility of the starting material in acetone and no reaction was detected. We applied

similar procedures with acetal *t*-**184**e dissolved in DCM or DCE at a range of different temperatures (Entries b-d), but no reaction took place. Following a procedure from Daniewsky,[178] the oxidation was tried using acetic acid in biphasic system DCM/H_2O (Entry e), after an overnight reaction, only starting material was identified; the temperature of the reaction was then increased to 45 °C but reaction did not start either. The reaction was also set up with the same reagents and as the acetal was soluble in hot acetic acid, it was used as solvent (Entry f); once again no reaction could be detected and only starting material was recovered.

At that point we decided to follow a two-step deprotection-oxidation sequence to obtain the corresponding β-ketosulfoximine **174** and at the same time, we chose to modify our approach and to synthesise acetal **184** as a diastereomeric mixture by another route starting from lactone **178** (Scheme 149).



Scheme 149

The DIBAL reduction of **178** afforded lactol **185** in quantitative yield, as a 0.6:1 ratio of diastereomers in deuterated chloroform solution, which was used without purification for the next step. Acetal **186** resulting from protection of the lactol with trimethyl orthoformate, was oxidised with *m*-CPBA to give a diastereomeric mixture of sulfoxides **183** in 89% yield; the corresponding sulfone was the major by-product of the reaction (up to 22% depending on the reaction) and was obtained as two diastereomers (Figure 32). Copper-catalysed imination led to the corresponding sulfoximine **184** in 79% yield.

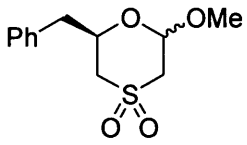
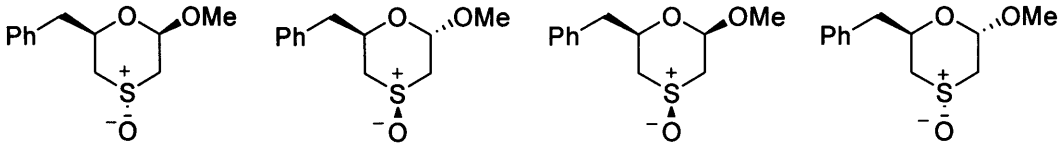


Figure 32

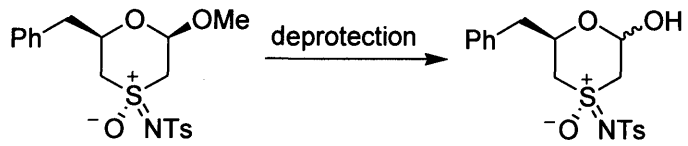
Acetal **186** was used as a mixture of isomers for the oxidation step, but both could be separated by flash chromatography on silica. Sulfoxide **183** resulting from the oxidation of **186**, was obtained as a diastereomeric mixture of compounds *t*-**183**e/*c*-**183**a/*c*-**183**e/*t*-**183**a in a 1/0.6/0.6/0.2 NMR ratio (Figure 33); the mixture was purified by flash chromatography on silica to give a fraction containing *t*-**183**e/*c*-**183**a/*c*-**183**e and a far more polar second fraction being the isomer *t*-**183**a. The sulfoximination reaction was set up using separately the mixture *t*-**183**e/*c*-**183**a/*c*-**183**e and *t*-**183**a as starting materials.



t-**183**e *c*-**183**a *c*-**183**e *t*-**183**a

Figure 33

We considered then the synthesis of β-ketosulfoximine **174** in two steps, first the deprotection of acetal **184** (Scheme 150) followed by oxidation of the resulting lactol. The first experiments on the deprotection, as for Jones oxidation, were investigated with acetal *t*-**184**e that can be obtained as a single isomer following the route described previously in Scheme 147.



t-**184**e *t*-**181**

Scheme 150

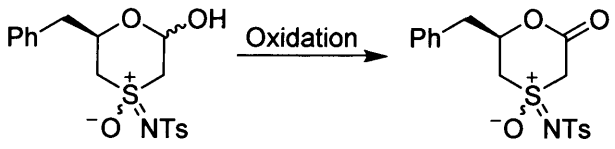
Table 24

Entry	Procedure	Results
a	*p*-TsOH, MeCN/H_2O, RT	No reaction
b	H_2SO_4 15% in H_2O/THF, RT then 60 °C	No reaction
c	TfOH, AcOH, 80 °C, 4 h	Starting material disappeared
d	TfOH (1M aqueous solution) AcOH, 80 °C, 24 h	*t*-**181** (81-98% yield)

Following extensive experimentation summarised in Table 24, it was found that the lactol ether of *t*-**184**e could be hydrolysed by heating in an aqueous solution of triflic and acetic acids to afford *t*-**181** as a mixture of isomers (Entry d).

Deprotection of the mixture of diastereomeric acetals **184** was achieved with the same procedure and lactol **181** were obtained as a mixture of isomers in 98% yield.[182]

Oxidation of lactol **181** to lactone **174** (Scheme 151) has not been straightforward and several oxidation methods have been tried (Table 25).



181 **174**

Scheme 151

Table 25

Entry	Reaction conditions	Results
a	PCC (1.0 to 1.7 eq.), M.S. 4Å, DCM 0 °C to RT, 20 to 72 h	lactone **174** (*cis* and *trans*), low mass recovery, 7% yield
b	DMP (1.0 to 3.0 eq.), DCM, RT, 1 to 20 h	lactone **174** (*cis* and *trans*), 20% yield; decomposition in the presence of a base
c	TEMPO (0.15 eq.), PhIOAc (1.5 eq.) DCM, RT	decomposition
d	NIS (5.0 eq.), TBAI (2.0 eq.), DCM, RT	decomposition
e	$(COCl)_2$ (1.1 eq.), Et_3N (5.0 eq.), DMSO (2.2 eq.), DCM, RT	decomposition
f	MnO_2 (15 eq.), EtOAc, RT, 8 days	starting material
g	Br_2 (1.1 to 3.5 eq.), $BaCO_3$ (1 to 3 eq.) dioxane/H_2O 3:1 and 1:3, RT, 3 to 5 h	sulfoximine **187** (2 diastereoisomers) 67% yield

Oxidation with PCC[183] (Entry a) led to the identification of both lactones on TLC and crude ^1H NMR. Monitoring of the reaction by TLC was easy and the method seemed promising apart for a long reaction time; however the laborious work-up led to considerable loss of material. Extraction of the organic compounds from the black dry residue (chromate) has been problematic and despite several trials to improve the work-up of this reaction, isolation of both lactones was achieved in only 7% yield. A long reaction time that could

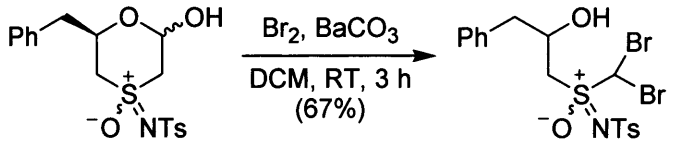
lead to some decomposition and a difficult work-up to extract the products made us search for other oxidants.

Dess-Martin oxidation[184] (Entry b) required some optimisation of the load of oxidant to prevent decomposition of the starting material or the product, but the lactones were isolated in 20% yield; that was finally the best yield we were able to obtain. The addition of pyridine to the reaction mixture led to complete decomposition and no starting material or product was detected in the crude mixture.

Oxidation with TEMPO[185] (Entry c) or NIS (Entry d) as well as Swern oxidation[186] (Entry e) did not yield any useful results; in some cases open-form products were identified showing that lactol **181** or lactone **174** was unstable under the reaction conditions.

Lactol **181** was inert when manganese oxide was used as the oxidant (Entry f).

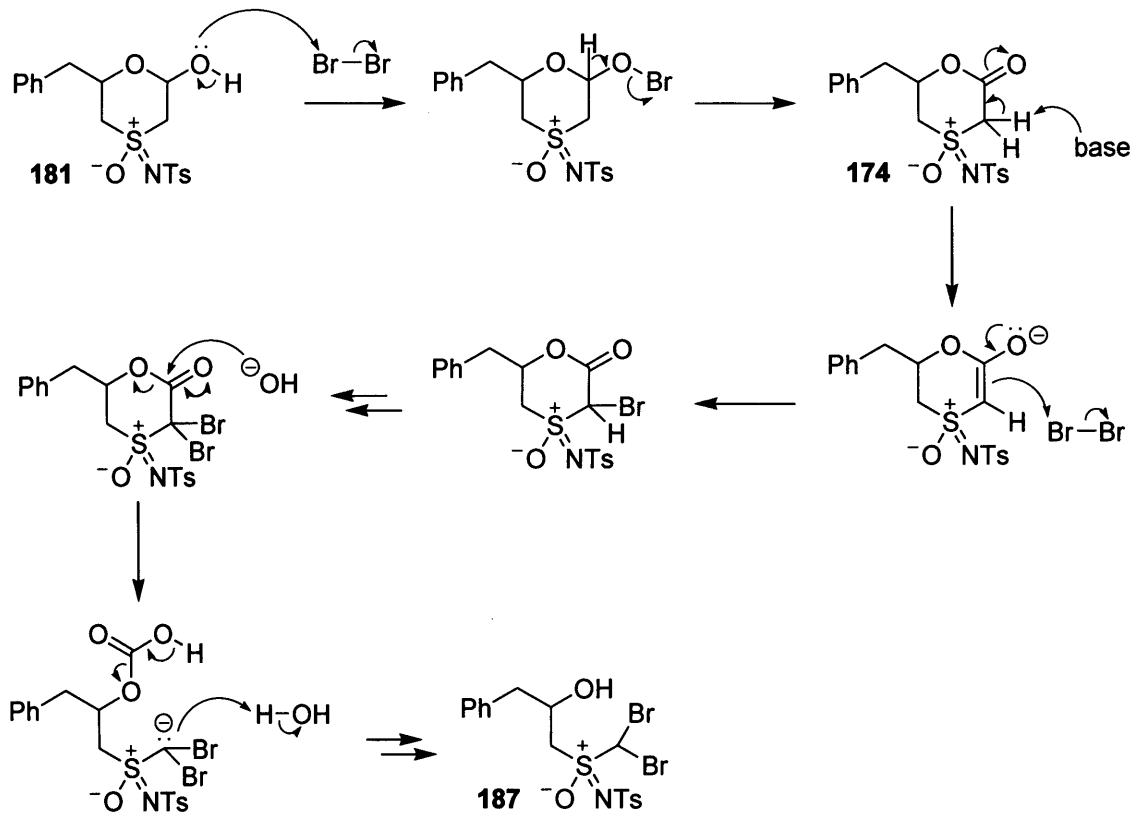
The most interesting result was the oxidation with bromine[187] (Scheme 152, Table 25, entry g) that led, after some adjustments to the procedure, to the formation of sulfoximine **187** in 67% yield, as a mixture of diastereomers.



181 **187**

Scheme 152

The structure lost a fragment corresponding initially to the lactone carbonyl and gained two bromine atoms on the carbon which was in the α-position of the carbonyl, these two facts suggest that a haloform-type reaction took place and thus oxidation of the lactol to the lactone was successful (Scheme 153). However, we have not been able to separate both reactions and systematically oxidation followed by decarboxylation occurred.



Scheme 153

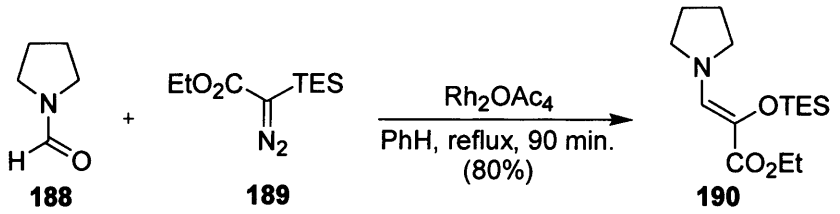
Even though we manage to synthesise cyclic β-ketosulfoximine **174** as two separable diastereomers, the low yield of the oxidation step (with DMP on a half-gram scale, 20% yield for both diastereomers) afforded enough material for characterisation only, for that reason we could not try diazo transfer on this substrate.

2.5. Novel diazosulfones

Given the difficulties which had been encountered in our original goal of synthesising the previously unknown diazosulfoximines, and the fact that diazosulfones, although perhaps under-utilised, were a known class of compounds, we decided to expand the scope of the project through investigation of some novel diazosulfone chemistry.

2.5.1. Silylated diazosulfones

Previous work in our and other laboratories[188-190] have shown that *C*-silylation of diazoesters expands the scope of chemistry which can be carried out.

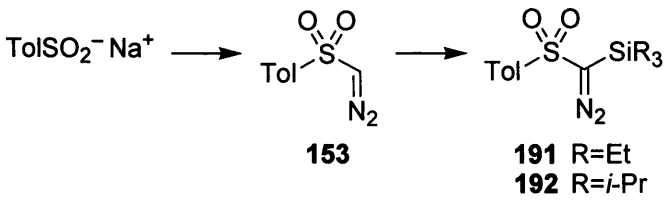


Scheme 154

When **188** and **189** are heated in benzene in the presence of rhodium(II) diacetate dimer (0.4 mol%), the major product obtained is the vinylogous carbamate **190** (Scheme 154). This product arises from reaction of the intermediate metal carbene with the formamide oxygen followed by rearrangement.

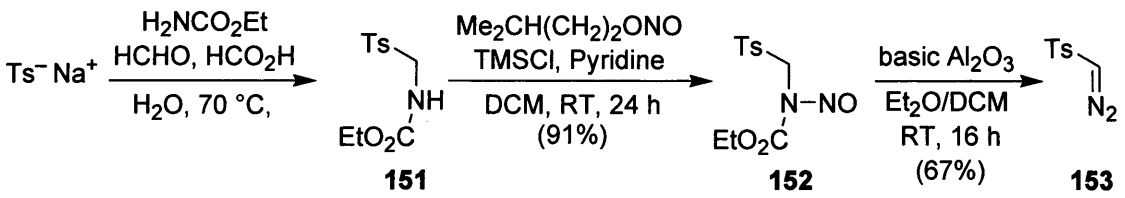
We wondered if in the case of diazosulfones, *C*-silylation would also lead to new applications of these compounds; we therefore commenced a study to discover whether a similar modification of reactivity was observed.

The obtention of silylated diazosulfones **191** and **192** was achieved through the synthesis of tosyldiazomethane **153** followed by silylation (Scheme 155).



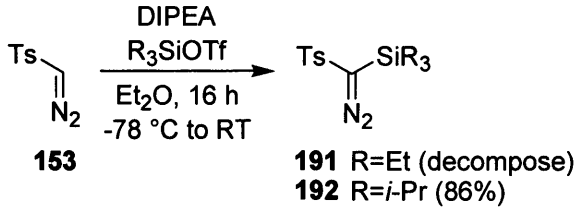
Scheme 155

Tosyldiazomethane **153** was prepared by Uguen's procedure[164] already described in a previous chapter (Cf 2.2, p104), starting from sodium toluenesulfinate (Scheme 156).



Scheme 156

We were delighted to find that silylation, as with diazoesters,[191, 192] could easily be effected using triethyl or triisopropylsilyl triflate and Hünig's base (DIPEA), to give silylated diazosulfones **191** and **192** (Scheme 157).

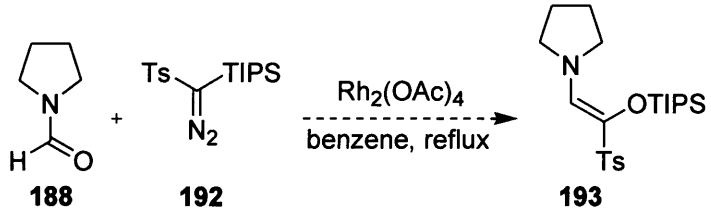


Scheme 157

Silylated diazosulfone **191** synthesised by this procedure was identified in the crude mixture along with some unreacted starting material; all attempts of purification through column chromatography on silica or alumina, or recrystallisation from the crude material, led to decomposition. The product also decomposed upon standing at room temperature (15 °C) overnight under high vacuum. We thought that compound **191** could be too sensitive towards hydrolysis and thus we chose to synthesise a more stable derivative, triisopropyl silylated diazosulfone **192**, in which the silicon atom would be less sterically accessible.

Upon the same treatment, tosyldiazomethane **153** was successfully converted to the silane **192b** in 86% yield, as yellow needles after purification by chromatography on silica and recrystallisation from hexane.

However, attempts to utilise the latter in the formamide olefination reaction previously developed in our group did not lead to alkene **193** (Scheme 158) but only to the recovery of starting materials.

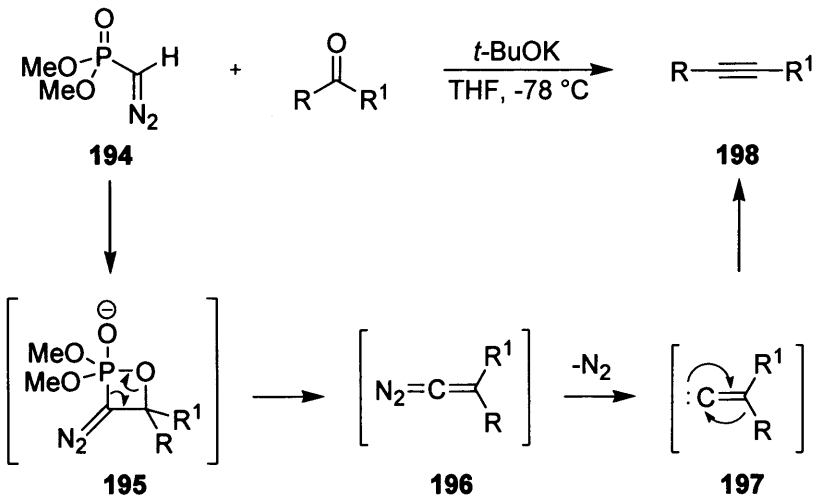


Scheme 158

In this project we have not been able to apply the formamide olefination reaction due to the stability of the starting materials; on the one hand TES derivative **191** decomposed too fast and could not be exploited, on the other hand TIPS derivative **192** was inert to all conditions tried. As we finally could not find a way to initiate the reaction, we decided to abandon this project.

2.5.2. A sulfur equivalent of the Gilbert-Seyferth reagent

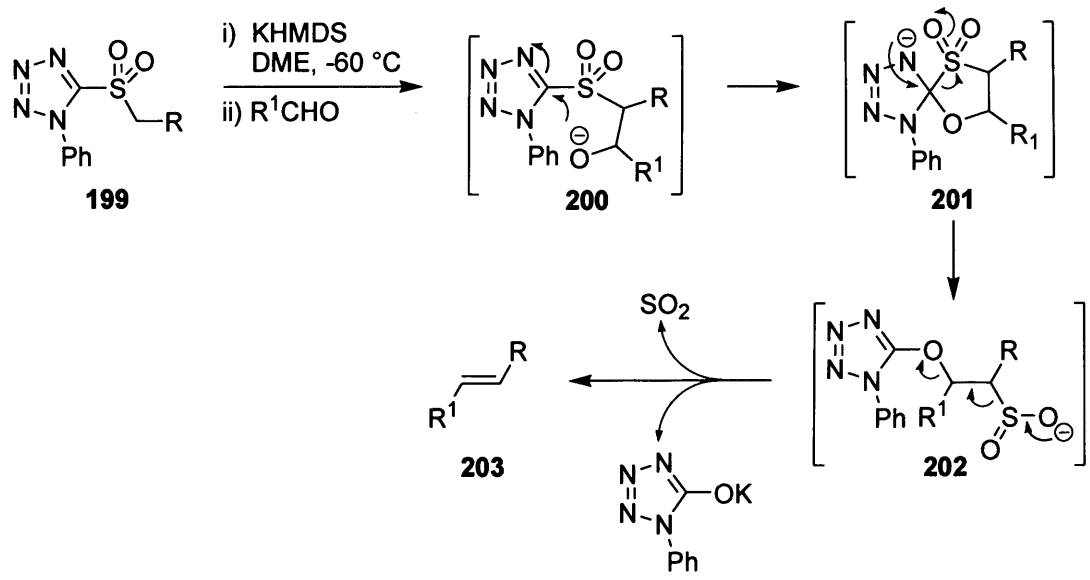
The Gilbert-Seyferth reagent, dimethyl (diazomethyl)phosphonate[193] **194** or diethyl (diazomethyl)phosphonate,[194] is used to convert aldehydes (or ketones) into alkynes **198** with an additional carbon atom (Scheme 159);[194, 195] it can also be used to generate vinylidene carbenes from ketones.[196, 197]



Scheme 159

It is presumed that the mechanism is Wadsworth-Emmons-like and involves initial formation of adduct **195**. Elimination of dimethyl phosphate leads via the diazo intermediate **196** to an alkylidene carbene **197**, which undergoes a 1,2-rearrangement to give the alkyne **198**. Although **194** has been a popular reagent for synthesis and the one-carbon homologation itself proceeds quite efficiently, researchers often opt for alternative strategies because of the multistep synthetic procedure required to prepare it.

We were interested in developing a sulfur-based hybrid of this reagent which we expected to behave in a similar way to the Gilbert-Seyferth reagent, but which could have enhanced reactivity, stability, and ease of use. Furthermore, the type of compounds we aimed to synthesise, can be compared to Julia-Kocienski olefination reagents,[198, 199] used to generate alkenes **203**. Julia-Kocienski olefination is a modified Julia olefination which uses 1-phenyl-1*H*-tetrazol-5-yl sulfone **199** as reagent (Scheme 160).

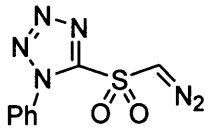


Scheme 160

Deprotonation of **199** followed by reaction with an aldehyde gives compound **200** which rearranges to **202** through a spirocyclic intermediate **201**; extrusion of sulfur dioxide and elimination of the tetrazole fragment leads to alkene **203**.

This variant is distinguished by the ability to provide high levels of *trans* selectivity in the absence of biasing electronic or steric factors. A combination of DME as solvent and KHMDS as base often provides optimal conditions for the synthesis of simple *trans* alkenes *via* the phenyltetrazole-variant.

Therefore, in the light of this chemistry, we wished to synthesise the diazomethyl sulfone **204** (Figure 34).

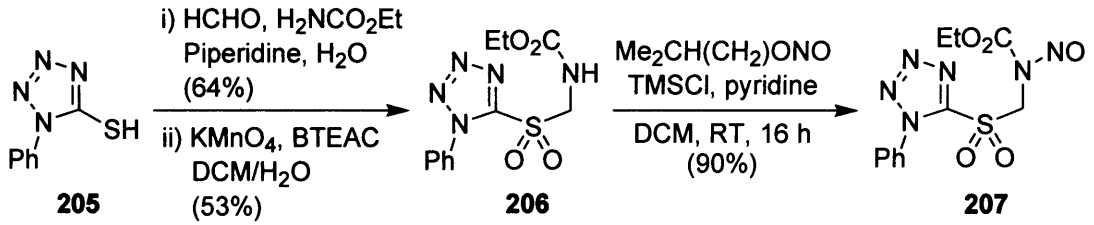


204

Figure 34

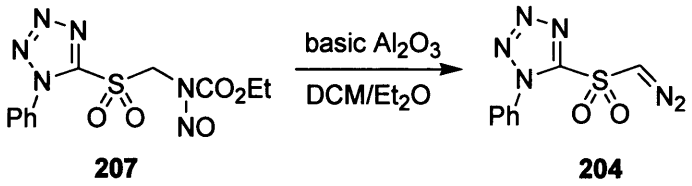
1-Phenyltetrazole-5-thiol **205** was converted to carbamate **206** by condensation with formaldehyde and urethane in the presence of piperidine, followed by oxidation with

potassium permanganate under phase-transfer conditions using benzyltriethylammonium chloride. Nitrosation using Uguen's conditions[164] afforded the crystalline sulfone **207** in 90% yield (Scheme 161).



Scheme 161

On treatment with basic alumina (Scheme 162), this material was seen to disappear; however, diazosulfone **204** could not readily be isolated.



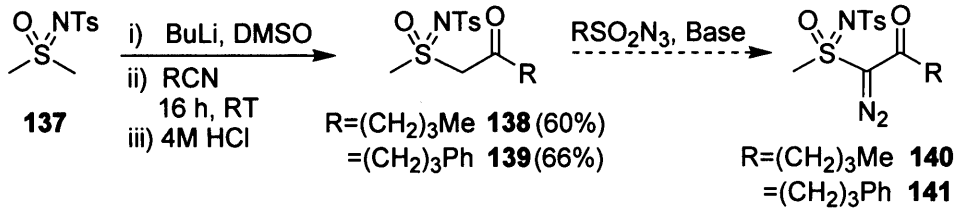
Scheme 162

Attempts to use the crude material to convert aldehydes to alkynes also proved fruitless.

3. Conclusion

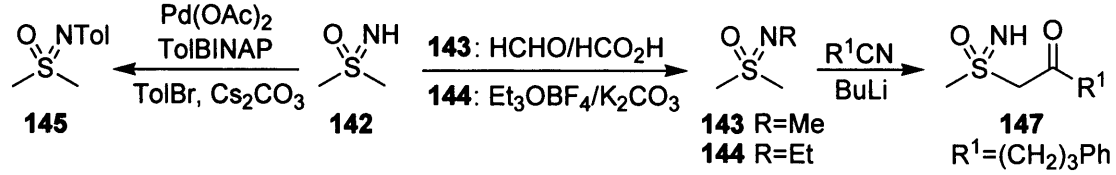
Towards acyclic α-diazosulfoximines

Racemic β-ketosulfoximines **138** and **139**, used as starting material for the project, were prepared by the method of Johnson,[159] and we quickly found that all attempts to convert **138** and **139** to the corresponding diazo compounds **140** and **141** were uniformly unsuccessful (Scheme 163).



Scheme 163

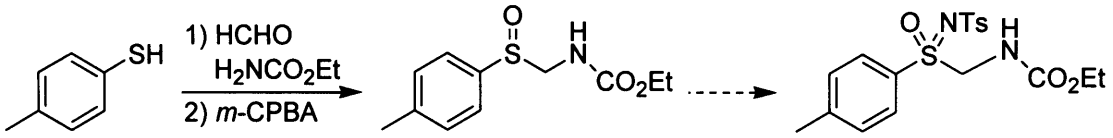
A range of bases, diazo transfer reagents, solvents and temperatures were investigated with **139** and in all cases, while the starting material was consumed, none of the desired products were isolated. In some cases, the sulfonamide corresponding to the diazo transfer reagent *was* obtained, suggesting that diazo transfer had taken place but that the product **141** was unstable. To modify the structure of the β-ketosulfoximine intermediate, we decided to vary the nature of the substituent on nitrogen, in the hope that this might lead to a more stable diazo compound (Scheme 164).



Scheme 164

Conversion of the *N*-alkylsulfoximines **143** and **144** to the corresponding β-keto derivatives was accompanied, unexpectedly, by loss of the *N*-alkyl substituent and moreover, attempted conversion of **145** to the corresponding ketosulfoximine was unsuccessful.

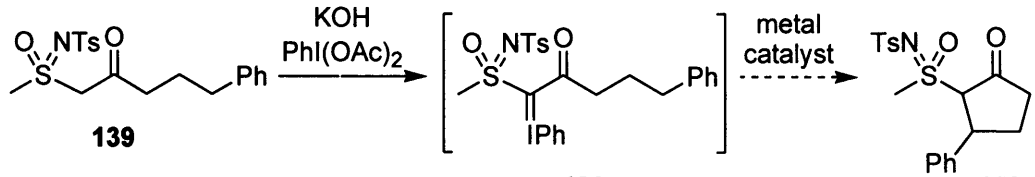
We decided then to try an alternative route (Scheme 165) through nitroso derivatives to synthesise diazosulfoximine. Numerous diazo compounds have also been prepared by reaction of primary amines or secondary carbamates with nitrosating reagents; therefore, following a recent procedure for the preparation of tosyldiazomethane, three-component condensation of 4-methylbenzenethiol **154** with formaldehyde and ethyl carbamate afforded secondary carbamate and sulfoxidation with *m*-CPBA was successful to give **156**. However, all sulfoximination protocols were unsuccessful to convert sulfoxide to the corresponding sulfoximine **157**, extensive decomposition occurred in short time.



154 **156** **157**

Scheme 165

At this stage, we wished to explore the possibility of generating metal carbenes from sulfoximines through iodonium ylides (Scheme 166). These species are readily available through the reaction of active methylene compounds with hypervalent iodine reagents, and react with rhodium and copper catalysts to generate metal carbenes.[165, 166]

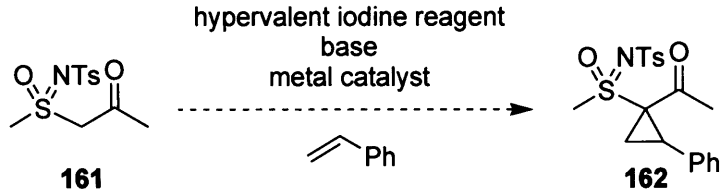


139 **158** **159**

Scheme 166

Initially when we tried to convert β-ketosulfoximine **139** to a phenyliodonium ylide **158**, the characteristic AB system of the starting material disappeared from the ^{1}H NMR spectrum, suggesting successful formation of iodonium ylide **158** had occurred. However, upon attempted purification of the reaction mixture by chromatography, decomposition occurred and full characterisation of **158** proved impossible. All attempts to utilise the **158** without purification were equally unsuccessful and did not give any isolable products.

Iodonium ylides can be generated as unisolated intermediates from β-dicarbonyl compounds[169, 170] and from α-nitroesters[171, 172] and in the presence of an alkene such as styrene, cyclopropanes may be formed directly; we tried to carry out this chemistry on β-ketosulfoximines (Scheme 167).



161 **162**

Scheme 167

Reaction of ketosulfoximine **161** with styrene and various hypervalent iodine reagents, bases and catalysts did not yield any of the desired cyclopropane **162**. In a further attempt to explore the utility of such conditions for the synthesis of sulfur-substituted cyclopropanes, a methyl sulfone and a phenyl sulfone corresponding to the sulfoximine **161** were also subjected to the same reaction conditions. No cyclopropanation was observed with either of these reagents (although cyclopropanation of styrene with dimethyl malonate *was* successful, as reported in the literature).

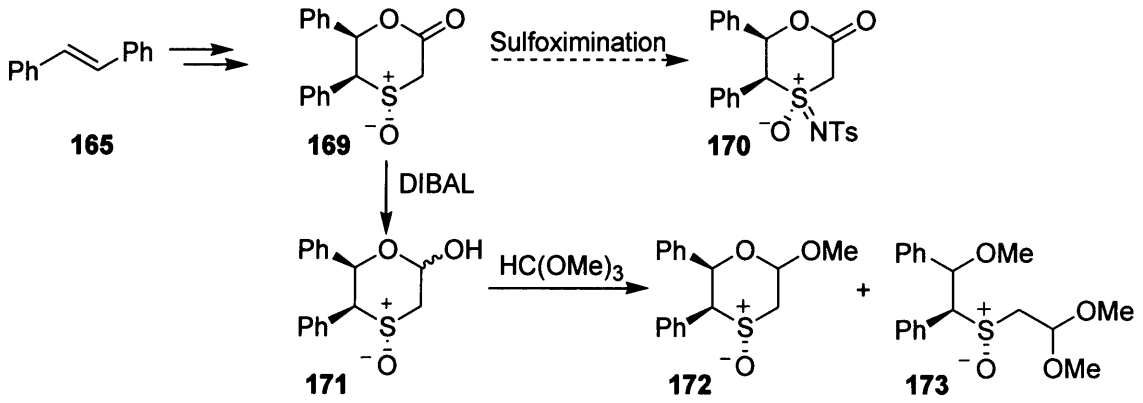
The stability of ketosulfoximines, in the reaction conditions for diazo transfer or for generating iodonium ylides, seems to be the major problem encountered during the work undertaken to synthesise acyclic α-diazo-β-ketosulfoximines. Although diazo transfer seemed successful, as well as formation of iodonium ylide, the characterisation of these carbene precursors was not possible. Attempts to utilise these species without isolating

them were fruitless and in most cases, no reaction was detected. Therefore, we have not been able to obtain valuable information on the decomposition pathway of the sulfoximidoyl carbenes.

Having failed to generate an acyclic α-diazo-β-ketosulfoximine, and with the suspicion that such species may be somewhat unstable, we decided to turn our research efforts in other directions to circumvent this instability by synthesising a cyclic α-diazo-β-ketosulfoximine.

Towards cyclic α-diazosulfoximines

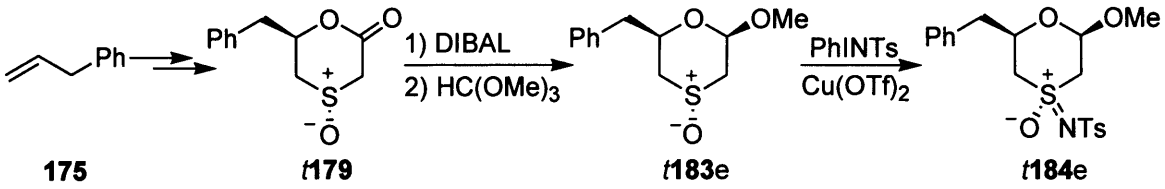
In her 1998 paper outlining the isolation of cyclic diazosulfoxides, Maguire described a route to the diazosulfoxide **169**.[9] Sulfoxide **169** was synthesised starting from stilbene **165** (Scheme 168), according to Maguire's paper and subjected to the conversion to the corresponding sulfoximine **170**; however, all attempts to convert this sulfoxide to a sulfoximine failed.



Scheme 168

To remove the interference from the lactone carbonyl, **169** was reduced to the lactol **171**, but subsequent protection as acetal **172** was complicated by the formation of **173** as the major product. This product was presumed to arise due to the ready formation of a benzylic cation, and for this reason a different cyclic sulfoximine was targeted.

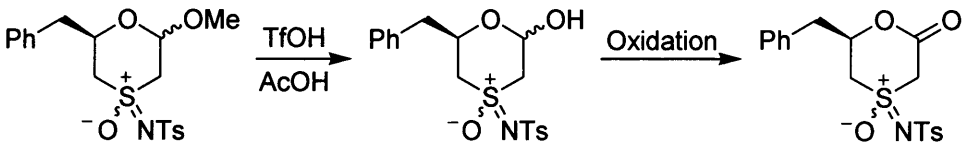
Allylbenzene **175** was converted to mixture of diastereomeric sulfoxides **179** as previously (Scheme 169). Both sulfoxides were separated and the following sequence of steps was carried out and optimised on the *trans* series. DIBAL reduction of *t*-**179** followed by the protection of the resulting lactol as an ether, led to acetal *t*-**183**e; imination gave the corresponding sulfoximine *t*-**184**e in high yield.



175 *t***179** *t***183e** *t***184e**

Scheme 169

Following extensive experimentation, it was found that the lactol ether of *t*-**184**e could be hydrolysed by heating in an aqueous solution of triflic and acetic acids to afford *t*-**181**, the same procedure was applied to the diastereomeric mixture **184** (Scheme 170).



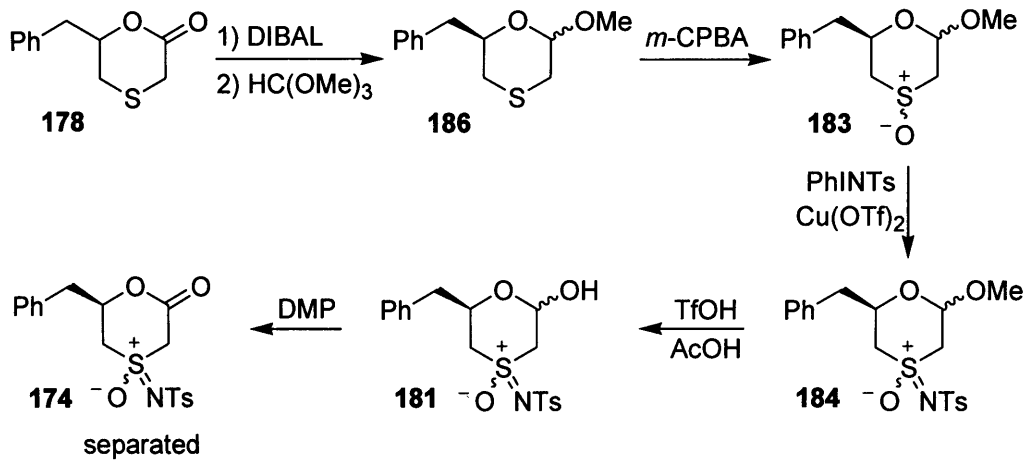
184 **181**

Scheme 170

However, oxidation of the lactol to the corresponding lactone with a variety of reagents was rather inefficient (up to 20% yield for the last step), and insufficient material could be obtained to attempt diazo transfer. However the two diastereomers of the resulting sulfoximine **174** were separated and identified, which made it possible to simplify the synthetic route.

In this sequence of steps leading to the cyclic sulfoximine **184**, two major drawbacks had to be overcome; the inconvenient separation of the diastereomers *t*-**179** and *c*-**179**, and the major side-reaction to the DIBAL reduction of the lactone **179** to the lactol **180**,

which resulted in the reduction of the sulfoxide to the sulfide. We decided then to change the order of the steps, reduction and of the carbonyl and subsequent protection as ether, followed by the oxidation of the sulfur and the imination (Scheme 171).

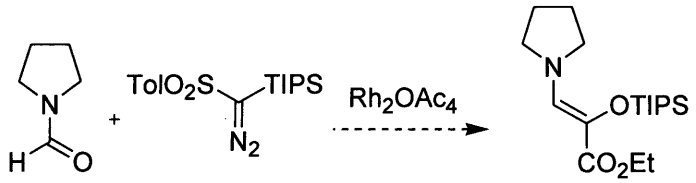


Scheme 171

The new route greatly simplified this synthesis, but unfortunately the low yield (20%) of the oxidation of the carbonyl could not be improved.

Novel diazosulfones

Given the difficulties which had been encountered in our original goal of synthesising the previously unknown α-diazosulfoximines, we decided to expand the scope of the project through investigation of some novel diazosulfone chemistry in relation to the formamide olefination reaction previously developed in our group (Scheme 172). Therefore, we aimed to discover if the *C*-silylation of diazosulfones led a similar modification of reactivity.

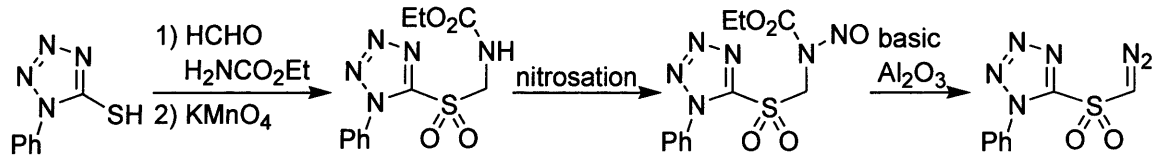


188 **192** **193**

Scheme 172

Starting from tosyldiazomethane, prepared by a literature procedure[164] from sodium toluenesulfinate, silylation was effected using a silyl triflate and Hünig's base to give silane **192**, the sulfone equivalent to compound **189**. However, attempts to utilise these compounds in the formamide olefination reaction led not to the desired product but only to recovery of starting materials.

In parallel, we also tried to develop a hybrid of the Gilbert-Seyferth reagent, diethyl (diazomethyl)phosphonate **194**, and the Julia-Kocienski olefination reagent, 1-phenyl-1*H*-tetrazol-5-yl sulfone **199**, which we expected to behave in a similar way but which could have enhanced reactivity, stability, and ease of use. Diazosulfone **204** was the targeted hybrid compound (Scheme 173).



205 **206** **207** **204**

Scheme 173

1-Phenyltetrazole-5-thiol **205** was converted to carbamate **206** by condensation with formaldehyde and urethane, followed by oxidation with potassium permanganate under phase-transfer conditions. Nitrosation using Uguen's conditions[164] afforded sulfone **207** which on treatment with basic alumina, was seen to disappear; however, diazosulfone **204** could not be isolated. Attempts to use the crude material to convert aldehydes to alkynes also proved fruitless.

4. Experimental

4.1. General Experimental Procedures

Melting points were obtained using a Reichert-Jung thermovar hot stage apparatus and are uncorrected.

Proton NMR spectra were recorded at 300 MHz on a Bruker AMX300 spectrometer, at 400 MHz on a Bruker AMX400 spectrometer or at 500 MHz on a Bruker AVANCE500 spectrometer. Chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; st, sextet; m; multiplet and br, broad. Coupling constants are recorded in Hertz to the nearest 0.1 Hz.

Carbon-13 NMR spectra were recorded at 75 MHz on a Bruker AMX300 spectrometer, at 100 MHz on Bruker AMX400 spectrometer or 125 MHz on Bruker AVANCE500 spectrometer. Chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Where necessary, carbon atoms were assigned using DEPT, HMQC and HMBC experiments.

Infrared spectra were recorded as thin films, KBr plate or DCM casts on a SHIMADZU FT-IR 8700 Fourier transform spectrometer. Major features of each spectrum are reported.

Low-resolution and high-resolution mass spectra were recorded by the University of London Intercollegiate Research Service and by John Hill (UCL chemistry department service). Low-resolution mass spectra were recorded on a Micromass 70-SE spectrometer and a Micromass ZAB-SE spectrometer using chemical ionisation (CI) or desorptional chemical ionisation (DCI), electron impact (EI), fast atom bombardment (FAB) or electrospray ionisation (ESI). Only molecular ions, fragments from molecular ions and major peaks are reported. High-resolution mass spectra were recorded on a Micromass 70-SE spectrometer.

Microanalyses were performed by Mrs. J. Maxwell, Christopher Ingold Laboratories on a Perkin Elmer 2400 CHN elemental analyser.

Flash chromatography was carried out on BDH silica gel (40-63 μm), Aldrich neutral aluminium oxide (deactivated with 6 wt% water (Grade III), *ca.* 150 mesh) or Acros Florisil® (100-200 mesh). Thin phase chromatography was performed on pre-coated, aluminium-backed normal phase Merck gel 60 F_{254} silica plates. Components were visualised by the quenching of u.v. fluorescence (λ_{max} 254 nm) as well as staining with iodine, vanillin, anisaldehyde or potassium permanganate, all followed by heat.

All reactions in non-aqueous solution were performed under an inert atmosphere of argon, using anhydrous solvents. All glassware was oven-dried (120 °C) and the glassware used for moisture sensitive reactions was flame dried and cooled under argon atmosphere prior to use.

All solvents were distilled before use when reactions were performed in anhydrous conditions. Anhydrous DCM, benzene, toluene and diisopropylamine were obtained by distillation from calcium hydride under a nitrogen atmosphere. Anhydrous diethyl ether (referred as ether) and THF were obtained by distillation from sodium/benzophenone ketyl under a nitrogen atmosphere. Anhydrous DMSO and DMF were obtained by stirring over calcium hydride followed by distillation under reduced pressure. Anhydrous acetonitrile was obtained by stirring over phosphorus pentoxide followed by distillation. Petroleum ether (referred as PE) is the fraction of light petroleum ether boiling between 30-40 °C. Anhydrous solvents were also obtained from Anhydrous Engineering (USA) solvent system after drying on alumina granules or pellets.

All other reagents were purified in accordance with the methods described in D. D. Perrin and W. L. F. Armarego, "Purification of laboratory chemicals", Pergamon Press, Third edition, 1988 or used as obtained from commercial sources.

Chemicals were purchased from Sigma-Aldrich Co. Ltd., Lancaster, Fluka, Acros, Avocado and Strem.

4.2. Experimental Procedures

4.2.1. Reactants

[*N*-(*p*-Tolylsulfonyl)imino]phenyliodinane[45] PhINTs

To a solution of iodobenzene diacetate (1.00 g, 3.1 mmol) and potassium hydroxide (0.44 g, 7.8 mmol) in dry methanol (13 mL) at 0 °C, was slowly added *p*-toluenesulfonamide (0.53 g, 3.1 mmol), keeping the temperature below 10 °C during the addition. The reaction mixture was stirred at room temperature for 3 hours and poured into distilled water (40 mL). Upon standing 16 hours at 4 °C, the pale yellow precipitate thus formed was filtered, washed with distilled water and dried at room temperature in a vacuum dessicator to give phenyliodinane as a slightly yellow powder (0.79 g, 68 % yield).

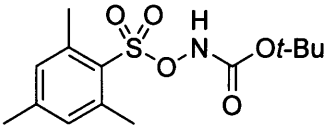
δ_H *(400 MHz, DMSO):* 2.26 (3H, s; C**H**$_3$), 7.05 (2H, d J=8.0; C**H** Phenyl), 7.28 (2H, t J=8.0; C**H** Phenyl), 7.44 (3H, m; C**H** Aromatic), 7.67 (2H, d J=7.2; C**H** Tolyl).
δ_C *(75 MHz, DMSO):* 20.8 (**C**H$_3$), 125.9, 129.2, 130.6, 137.1 (*o-/m-***C**H Aromatic), 126.1 (*p-***C**H Phenyl), 127.6 (**C** Phenyl), 130.1 (**C**-SO$_2$ Tosyl), 133.1 (CH$_3$-**C** Tosyl).

Tosyl azide[200] TsN$_3$

To a solution of tosyl chloride (3.33 g, 17.5 mmol) in acetone/water 1/1 (100 mL) at 0 °C was added sodium azide (1.14 g, 17.5 mmol) and the reaction mixture was stirred for 2 hours at 0 °C. Acetone was evaporated and the aqueous phase was extracted with ether (3x50 mL); the combined organic phases were washed with brine (150 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to give tosyl azide (3.22 g, 93% yield) as a colourless oil.

δ_H *(400 MHz, CDCl$_3$):* 2.47 (3H, s; C**H**$_3$), 7.39 (2H, d J=8.0; C**H** Tosyl), 7.82 (2H, d J=8.3; C**H** Tosyl).
δ_C *(100 MHz, CDCl$_3$):* 21.6 (**C**H$_3$), 127.4, 130.2 (**C**H Tosyl), 135.3 (**C**-SO$_2$ Tosyl), 146.2 (CH$_3$-**C** Tosyl).
IR (υ_{max} cm^{-1}, film, neat): 813, 896; 1169, 1371 (SO$_2$); 2129 (N$_3$); 2986, 3053.

O-Mesitylenesulfonyl-N-(*tert*-butyloxycarbonyl)hydroxylamine[28]



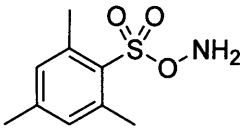
In a round-bottom flask fitted with a calcium chloride tube, to a solution of Boc hydroxylamine (0.50 g, 3.8 mmol) in dry DMF (2.5 mL), was added triethylamine (0.53 mL, 3.8 mmol) followed by the addition in small portions of mesitylenesulfonyl chloride (0.82, 3.8 mmol). The reaction mixture was stirred at room temperature for 1 h after the addition and poured into ice-water. The aqueous phase was extracted with DCM (3x20 mL), the combined organic phases washed with water (50 mL), brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica (toluene, toluene/EtOAc 35/1) to give MSHBoc (0.53 g, 44% yield) as a pale yellow solid.

Rf: 0.25 (toluene/EtOAc 35/1).

δ_H *(300 MHz, $CDCl_3$):* 1.30 (9H, s; (CH_3)$_3$), 2.31 (3H, s; *p*-CH_3), 2.66 (6H, s; *o*-CH_3), 6.98 (2H, C**H** Mesitylene), 7.81 (1H, br s; N**H**).

δ_C *(75 MHz, $CDCl_3$):* 21.1 (*p*-**C**H_3), 23.1 (*o*-**C**H_3), 27.7 (C-(**C**H_3)$_3$), 83.8 (**C**-(CH_3)$_3$), 131.7 (**C**H Mesitylene), 141.9 (**C**-CH_3 Mesitylene), 144.4 (**C**-SO_3 Mesitylene), 154.3 (**C**=O).

O-Mesitylenesulfonylhydroxylamine[28]



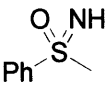
MSHBoc (220 mg, 0.7 mmol) was cooled to 0 °C in an ice-water bath and then dissolved in TFA (0.77 mL, 10.5 mmol). The reaction mixture was stirred for 10 minutes and poured into water. The precipitate thus formed was collected by filtration, washed with cold water and recrystallised from cold ether/hexane to obtain MSH (71 mg, 47% yield) as white needles.

δ_H *(300 MHz, $CDCl_3$):* 2.27 (3H, s; *p*-CH_3), 2.64 (6H, s; *o*-CH_3), 5.55 (2H, br s; NH_2), 7.00 (2H, C**H** Mesitylene).

δ_C *(75 MHz, $CDCl_3$):* 21.2 (*p*-**C**H_3), 22.8 (*o*-**C**H_3), 131.7 (**C**H), 141.0 (**C**-CH_3), 143.8 (**C**-SO_3).

4.2.2. Acyclic sulfoximines

S-Methyl-*S*-phenylsulfoximine 2[46]



To a solution of methyl phenyl sulfoxide **1** (200 mg, 1.43 mmol), trifluoroacetamide (322 mg, 2.85 mmol), magnesium oxide (229 mg, 5.71 mmol) and rhodium diacetate dimer (17 mg, 0.04 mmol) in dry DCM (20 mL), under argon atmosphere, was added iodobenzene diacetate (918 mg, 2.85 mmol) in small portions. The mixture was stirred at room temperature for 12 hours and filtered through a pad of celite which was washed with DCM (2x5 mL). The solvent was removed *in vacuo* and the residue dissolved in methanol (20 mL). Potassium carbonate (982 mg, 7.10 mmol) was added and the mixture was stirred at room temperature for 30 minutes. Methanol was evaporated and the crude purified by flash chromatography on silica (EtOAc/PE 80/20, EtOAc) to afford pure sulfoximine **2** as a yellow oil (166 mg, 75% yield).

Rf: 0.40 (EtOAc/PE 80/20).

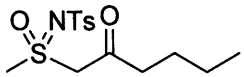
δ_H *(400 MHz, $CDCl_3$):* 2.58 (1H, br s; N**H**), 3.08 (3H, s; C$\mathbf{H}_3$), 7.48-7.55 (2H, m; *o-/m-*C**H** Phenyl), 7.59 (1H, m; *p-*C**H** Phenyl), 7.98 (2H, m; *o-/m-*C**H** Phenyl).

δ_C *(100 MHz, $CDCl_3$):* 46.0 (**C**H_3), 127.5, 129.1 (*o-/m-***C**H Phenyl), 132.9 (*p-***C**H Phenyl), 143.3 (**C** Phenyl).

m/z (EI): 125 (81), 140 (91), 155 (Me•, 62%).

IR (υ_{max} cm^{-1}, film, neat): 689, 745, 1099, 1221; 3271 (N-H).

S-Methyl-*N*-tosyl-*S*-(2-oxohexyl)sulfoximine 138[122]



To a solution of *S,S*-dimethyl-*N*-tosylsulfoximine **137** (500 mg, 2.0 mmol) in dry DMSO (5 mL) at room temperature under argon atmosphere was added dropwise butyllithium (1.50 mL, 1.6 M in hexane, 2.4 mmol) followed by valeronitrile (0.36 mL, 2.4 mmol). The reaction mixture was stirred 16 hours at room temperature and poured into with ice-water (50 mL); the precipitate thus formed was filtered through celite and washed with chloroform. The organic phase was washed once with water, dried over magnesium

sulfate, filtered and concentrated *in vacuo*. The pasty residue was dissolved in 4M hydrochloric acid (5 mL) and heated under reflux for 30 minutes. The reaction mixture was diluted with water (50 mL), the product was extracted with chloroform (2x100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Recrystallisation from methanol gave sulfoximine **138** as colourless crystals (398 mg, 60% yield).

Rf: 0.45 (EtOAc/PE 60/40).

δ_H *(500 MHz, $CDCl_3$):* 0.90 (3H, t J=7.3; CH_2-C**H**$_3$), 1.32 (2H, st J=7.4; CH_2-C**H**$_2$-CH_3), 1.58 (2H, qt J=7.3; CH_2-C**H**$_2$-CH_2), 2.39 (3H, s; C**H**$_3$ Tosyl), 2.68 (1H, dt J=18.3, 7.3; O=C-**H**CH-CH_2), 2.77 (1H, dt J=18.3, 7.3; O=C-HC**H**-CH_2), 3.32 (3H, s; N(O)S-C**H**$_3$), 4.48 (1H, d J=14.7; N(O)S-**H**CH-C=O), 4.67 (1H, d J=14.7; N(O)S-HC**H**-C=O), 7.26 (2H, d, J=8.0; *m*-C**H** Tosyl), 7.81 (2H, d, J=8.3; *o*-C**H** Tosyl).

δ_C *(125 MHz, $CDCl_3$):* 13.7 (CH_2-**C**H_3), 21.5 (**C**H_3 Tosyl), 21.9 (CH_2-**C**H_2-CH_3), 24.9 (CH_2-**C**H_2-CH_2), 42.8 (N(O)S-**C**H_3), 44.8 (O=C-**C**H_2-CH_2), 63.7 (N(O)S-**C**H_2-C=O), 126.6 (*o*-**C**H Tosyl), 129.4 (*m*-**C**H Tosyl), 140.1 (**C**-SO_2 Tosyl), 143.2 (CH_3-**C** Tosyl), 198.9 (**C**=O).

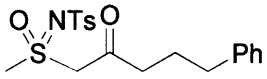
m/z (CI positive): 234 (10), 332 (MH^+, 100 %).

IR (υ_{max} cm^{-1}, DCM cast): 1045, 1089; 1153, 1319 (SO_2); 1724 (C=O); 2962.

Found: C 50.8, H 6.5, N 4.2. *Calculated for $C_{14}H_{21}NO_4S_2$:* C 50.7, H 6.4, N 4.2 %.

Melting Point: 95-97 °C (recrystallised from methanol).

S-Methyl-*N*-tosyl-*S*-(2-oxo-5-phenylpentyl)sulfoximine 139[122]



To a solution of *S,S*-dimethyl-*N*-tosylsulfoximine **137** (1.00 g, 4.0 mmol) in dry DMSO (10 mL) at room temperature under argon atmosphere was added dropwise *n*-butyllithium (3.0 mL, 1.6 M in hexane, 4.8 mmol) followed by 4-phenylbutyronitrile (0.71 mL, 4.8 mmol). The reaction mixture was stirred 16 hours at room temperature then poured into ice-water (100 mL); the precipitate thus formed was filtered through celite and washed with chloroform. The organic phase was washed with water (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The pasty residue was dissolved in 4M hydrochloric acid (10 mL) and heated under reflux for 30 minutes. The reaction mixture was diluted with water (100 mL), the product was extracted with chloroform

(2x150 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Recrystallisation from methanol gave sulfoximine **139** as white crystals (1.03 g, 66% yield).

Rf: 0.50 (EtOAc/PE 60/40).

δ_H (500 MHz, $CDCl_3$): 1.95 (2H, qt *J*=7.1; CH_2-C**H**$_2$-CH_2), 2.39 (3H, s; C**H**$_3$ Tosyl), 2.62 (2H, t *J*=7.5; CH_2-C**H**$_2$-Ph), 2.69 (1H, dt *J*=18.5, 7.1; O=C-**H**CH-CH_2), 2.79 (1H, dt *J*=18.6, 7.1; O=C-HC**H**-CH_2), 3.30 (3H, s; N(O)S-C**H**$_3$), 4.43 (1H, d *J*=14.9; N(O)S-**H**CH-C=O), 4.61 (1H, d *J*=14.7; N(O)S-HC**H**-C=O), 7.15 (2H, dd, *J*=8.2, 1.3; *o*-C**H** Phenyl), 7.18 (1H, tt *J*=7.4, 1.9; *p*-C**H**, Phenyl), 7.25-7.29 (4H, m; C**H** Aromatic), 7.81 (2H, d *J*=8.3; *o*-C**H** Tosyl).

δ_C (125 MHz, $CDCl_3$): 21.5 (**C**H_3 Tosyl), 24.5 (CH_2-**C**H_2-CH_2), 34.6 (**C**H_2-Ph), 42.8 (N(O)S-**C**H_3), 44.2 (O=C-**C**H_2-CH_2), 63.7 (N(O)S-**C**H_2-C=O), 126.2 (*p*-**C**H Phenyl), 126.6 (*o*-**C**H Tosyl), 128.5 (**C**H Phenyl), 129.4 (*m*-**C**H Tosyl), 140.0 (**C**-SO_2 Tosyl), 140.9 (**C** Phenyl), 143.2 (CH_3-**C** Tosyl), 198.5 (**C**=O).

m/z (FAB positive-methane): 234 (12), 338 (21), 394 (MH^+, 100 %).

HRMS (CI positive-methane, Instrument Resolution 6000): Required: 394.11467. Found: 394.11469. Error 0.05 ppm.

IR (υ_{max} cm^{-1}, DCM cast): 1064, 1089; 1153, 1319 (SO_2); 1496, 1600; 1724 (C=O); 2955.

Melting Point: 79-80 °C (recrystallised from methanol).

S,S-Dimethylsulfoximine 142[25]

Preparation of a solution of sodium anthracenide 0.6M in DME:

To a suspension of anthracene (6.47 g, 36 mmol) in distilled DME (60 mL) under argon atmosphere was added sodium (0.83 g, 36 mmol). The mixture was sonicated 2 hours to obtain a deep blue solution of sodium anthracenide (0.6 M).

Procedure for the reduction of the S,S-dimethyl-N-tosylsulfoximine:

To a suspension of *S,S*-dimethyl-*N*-tosylsulfoximine **137** (3.00 g, 12 mmol) in distilled DME (50 mL) at 0 °C (ice-water bath) was added dropwise sodium anthracenide solution until a deep blue colour persisted. Then at 0 °C, 3M hydrochloric acid (60 mL) was added

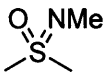
slowly and the mixture poured in DCM (150 mL). The acidic aqueous phase was extracted with DCM (3x50 mL) and ether (1x50 mL) and made basic with sodium carbonate. The water was removed *in vacuo*, the dry white residue was crushed in a thin powder and stirred with DCM (120 mL) for 2 hours. The suspension was filtered, washed with DCM (2x20 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the *NH*-sulfoximine **142** as a pale yellow solid (0.86 g, 77 % yield).

δ_H (400 MHz, $CDCl_3$): 2.81 (1H, br s; N**H**), 2.98 (6H, s; C**H**$_3$-S-C**H**$_3$).

δ_C (75 MHz, $CDCl_3$): 45.4 (**C**H_3-S-**C**H_3).

m/z (Desorptional CI positive-methane): 94 (MH^+, 100%).

N,S,S-Trimethylsulfoximine 143[86]



To a solution of *NH*-sulfoximine **142** (0.79 g, 9 mmol) in water (10 mL) was added formaldehyde (37% aqueous solution, 13.7 mL, 0.17 mol) followed by formic acid (64 mL, 1.7 mol). The reaction mixture was heated to reflux for 48 hours, cooled to room temperature and extracted with DCM (3x100 mL), the combined organic phases were washed with water (100 mL) and brine (150 mL), dried over magnesium sulfate, concentrated *in vacuo* and purified by flash chromatography on silica (MeOH/DCM 5/95) to give the sulfoximine **143** as a pale yellow oil (0.16 g, 20% yield).

Rf: 0.30 (MeOH/DCM 10/90).

δ_H (400 MHz, $CDCl_3$): 2.74 (3H, s; N-C**H**$_3$), 2.94 (6H, s; C**H**$_3$-S-C**H**$_3$).

δ_C (100 MHz, $CDCl_3$): 29.1 (N-**C**H_3), 40.9 (**C**H_3-S-**C**H_3).

HRMS (CI positive-methane, Instrument Resolution 6000): Required: 108.04831. Found: 108.04808. Error 2.13 ppm.

IR (υ_{max} cm^{-1}, DCM cast): 1107, 1229, 1327, 1417, 1454, 2808, 2885, 2928.

S,S-Dimethyl-N-Ethyl-sulfoximine 144[161]

To a solution of *NH*-sulfoximine **142** (100 mg, 1.1 mmol) in dry DCM (8 mL) cooled to 0 °C, was added anhydrous potassium carbonate (163 mg, 1.2 mmol) and triethyloxonium fluoroborate (224 mg, 1.2 mmol). The mixture was stirred at 0 °C for 1 hour and then at room temperature for 24 hours. Water (2 mL) was then carefully added and the mixture poured into cold water (5 mL). The product was extracted with DCM (3x10 mL), the aqueous phase was evaporated and the white dry residue was stirred in DCM for 15 hours with magnesium sulfate and filtered. The combined organic phases were concentrated *in vacuo* and purified by flash chromatography on silica (MeOH/DCM 5/95) to afford sulfoximine **144** as a pale yellow oil (66 mg, 51% yield).

Rf: 0.30 (MeOH/DCM 5/95).

δ_H *(300 MHz, $CDCl_3$):* 1.22 (3H, t *J*=7.2; CH_2-C**H**$_3$), 3.01 (6H, s; C**H**$_3$-S-C**H**$_3$), 3.13 (2H, q *J*=7.2; C**H**$_2$-CH_3).

δ_C *(75 MHz, $CDCl_3$):* 18.3 (CH_2-**C**H_3), 38.0 (**C**H_2-CH_3), 41.8 (**C**H_3-S-**C**H_3).

m/z (CI positive-methane): 94 (22), 106 (32), 122 (MH^+, 100%).

S,S-Dimethyl-N-tolyl-sulfoximine 145[102]

To a flame dried two necked flask fit with a condenser, charged with palladium diacetate (11 mg, 0.05 mmol) and TolBINAP (51 mg, 0.075 mmol) under argon atmosphere, was added dry toluene (10 mL); the mixture was stirred at room temperature until dissolution was complete. Then was added successively 4-bromotoluene (171 mg, 1.00 mmol), *NH*-sulfoximine **142** (116 mg, 1.25 mmol) and cesium carbonate (456 mg, 1.40 mmol). The reaction mixture was heated under reflux for 48 hours. The crude mixture was diluted with methyl *tert*-butyl ether and filtered through celite which was washed thoroughly with methyl *tert*-butyl ether. The organic phase was evaporated and the crude yellow oil was purified by flash chromatography on silica (EtOAc/PE 60/40 to 100%) to give the pure sulfoximine **145** in 8% yield (15 mg).

Rf: 0.45 (EtOAc/PE 60/40).

δ_H *(400 MHz, $CDCl_3$):* 2.29 (3H, s; C**H**$_3$ Tolyl), 3.13 (6H, s; C**H**$_3$-S-C**H**$_3$), 6.97 (2H, br dt *J*=8.3, 2.1; C**H** Tolyl), 7.05 (2H, br dt *J*=8.1, 2.8; C**H** Tolyl).

δ_C *(100 MHz, $CDCl_3$):* 20.7 (**C**H_3 Tolyl), 41.9 (**C**H_3-S-**C**H_3), 123.4-129.8 (**C**H Tolyl), 131.7 (N-**C**), 142.2 (**C**-CH_3).

m/z (CI positive-methane): 106 (100), 184 (MH^+, 63%).

N-phenyl-*S,S*-dimethylsulfoximine 146[102]

To a flame dried two necked flask fit with a condenser, charged with palladium diacetate (11 mg, 0.05 mmol) and TolBINAP (51 mg, 0.075 mmol) under argon atmosphere, was added dry toluene (10 mL); the mixture was stirred at room temperature until dissolution was complete. Then was added successively bromobenzene (105 μL, 1.00 mmol), *NH*-sulfoximine **142** (116 mg, 1.25 mmol) and cesium carbonate (456 mg, 1.40 mmol). The reaction mixture was heated under reflux for 48 hours. The crude mixture was diluted with methyl *tert*-butyl ether and filtered through celite which was washed thoroughly with methyl *tert*-butyl ether. The organic phase was evaporated and the crude yellow oil was purified by flash chromatography on silica (EtOAc/PE 60/40 to 100%) to give the pure product **146** in 15% yield (26 mg).

Rf: 0.25 (EtOAc/PE 60/40).

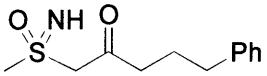
δ_H *(400 MHz, $CDCl_3$):* 3.13 (6H, s; C**H**$_3$-S-C**H**$_3$), 6.98 (2H, tt *J*=8.3, 1.1; *p*-C**H** Phenyl), 7.07 (2H, ddt *J*=8.1, 2.1, 1.3; *o*-C**H** Phenyl), 7.23 (2H, ddt *J*=8.4, 7.4, 2.0; *m*-C**H** Phenyl).

δ_C *(100 MHz, $CDCl_3$):* 41.9 (**C**H_3-S-**C**H_3), 122.2 (*p*-**C**H Phenyl), 123.3 (*o*-**C**H Phenyl), 129.2 (*m*-**C**H Phenyl), 145.0 (**C** Phenyl).

HRMS (CI positive-methane, Instrument Resolution 6000): Required: 169.05559. Found: 169.05527. Error 1.89 ppm.

IR (υ_{max} cm^{-1}, DCM cast): 1055, 1202, 1487, 1595.

_S_-Methyl-_S_-(2-oxo-5-phenylhexyl)sulfoximine 147[122]



To a solution of _S,S_-dimethyl-_N_-ethylsulfoximine **144** (73 mg, 0.6 mmol) in dry DMSO (1.2 mL) at room temperature under argon atmosphere was added dropwise _n_-butyllithium (0.56 mL, 1.6 M in hexane, 0.9 mmol) followed by 4-phenylbutyronitrile (107 µL, 0.7 mmol). The reaction mixture was stirred 16 hours at room temperature then 4M hydrochloric acid (3 mL) was added and the reaction mixture stirred for 2 hours at room temperature. The reaction mixture was extracted with chloroform (3x10 mL), the combined organic phases were washed with water (20 mL) and brine (20 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica (MeOH/DCM 2/98) gave product **147** in 34% yield (49 mg).

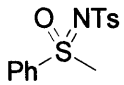
Rf: 0.25 (MeOH/DCM 2/98).

δ_H *(400 MHz, $CDCl_3$):* 1.95 (2H, qt J=7.2; CH_2-C**H_2**-CH_2), 2.60-2.65 (4H, m C**H_2**-CH_2-C**H_2**), 2.66 (3H, s; N(O)S-C**H_3**), 3.65 (1H, d J=13.6; N(O)S-**H**CH-C=O), 3.76 (1H, d J=13.6; N(O)S-HC**H**-C=O), 7.15-7.21 (3H, m; Phenyl), 7.27-7.30 (2H, m; C**H** Phenyl).

δ_C *(100 MHz, $CDCl_3$):* 24.5 (CH_2-**C**H_2-CH_2), 34.7 (**C**H_2-Ph), 39.0 (N(O)S-**C**H_3), 44.6 (O=C-**C**H_2-CH_2), 63.9 (N(O)S-**C**H_2-C=O), 126.1 (*p*-**C**H Phenyl), 128.4 (*o-/m*-**C**H Phenyl), 141.1 (**C** Phenyl), 202.1 (**C**=O).

IR (υ_{max} cm^{-1}, DCM cast): 1031, 1454; 1715 (C=O); 2876, 2933; 3418 (N-H).

_S_-Methyl-_S_-phenyl-_N_-tosylsulfoximine 148[44]



To a solution of copper(II) triflate (25 mg, 0.07 mmol) in dry acetonitrile (1.3 mL) under argon atmosphere, was added methyl phenyl sulfoxide **1** (100 mg, 0.71 mmol) followed, when dissolution was complete, by [N-(p-tolylsulfonyl)imino]phenyliodinane (293 mg, 0.78 mmol) in small fractions over 10 minutes. After 2 minutes the reaction mixture became clear, TLC (EtOAc/PE 60/40) showed completion and acetonitrile was evaporated *in vacuo*. The crude material was purified by flash chromatography on silica (EtOAc/PE 40/60) to afford sulfoximine **148** as white needles (179 mg, 81% yield).

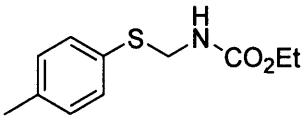
Rf: 0.30 (EtOAc/PE 40/60).

δ_H (300 MHz, $CDCl_3$): 2.38 (3H, s; C**H**$_3$ Tosyl), 3.41 (3H, s; N(O)S-C**H**$_3$), 7.24 (2H, d *J*=8.5; C**H** Tosyl), 7.58 (2H, m; *m*-C**H** Phenyl), 7.66 (1H, m; *p*-C**H** Phenyl), 7.83 (2H, m; *o*-C**H** Phenyl), 7.99 (2H, d *J*=8.2; C**H** Tosyl).

δ_C (100 MHz, $CDCl_3$): 21.4 (**C**H$_3$ Tosyl), 46.5 (N(O)S-**C**H$_3$), 126.6, 127.4, 129.2, 129.6 (*o*-/*m*-**C**H Phenyl), 134.3 (*p*-**C**H Phenyl), 138.2, 140.6, 142.8 (**C** Aryl).

m/z (CI positive-methane): 294 (30), 310 (MH^+, 100%), 338 (40).

Ethyl *N*-[(*p*-tolylsulfanyl)methyl]carbamate 155



To a solution of thiocresol **154** (15.0 g, 0.12 mol) in dry toluene (110 mL) were added successively urethane (10.7 g, 0.12 mol), paraformaldehyde (4.7 g, 0.16 mol) and 10 drops of piperidine. The mixture was heated under reflux for 18 hours with a Dean-Stark removal of water apparatus. The reaction mixture was cooled to room temperature and then to -18 °C. The crude carbamate precipitate formed was collected by filtration, washed with cold toluene (2x50 mL) and used without any further purification (20.9 g, 77% yield). However, recrystallisation from ethanol 99% gave pure carbamate **155** as white pellets which were used to run analyses.

Rf: 0.30 (EtOAc/PE 10/90).

δ_H (500 MHz, $CDCl_3$): 1.20 (3H, d *J*=7.0; CH_2-C**H**$_3$), 2.33 (3H, s; C**H**$_3$ Tolyl), 4.10 (2H, q *J*=6.9; C**H**$_2$-CH_3), 4.56 (2H, d *J*=6.5; S-C**H**$_2$-NH), 5.04 (1H, br t *J*=6.0; N**H**), 7.13 (2H, d *J*=7.7; C**H** Tolyl), 7.35 (2H, d *J*=8.0; C**H** Tolyl).

δ_C (100 MHz, $CDCl_3$): 14.5 (CH_2-**C**H$_3$), 21.1 (**C**H$_3$ Tosyl), 46.8 (S-**C**H$_2$-NH), 61.2 (**C**H$_2$-CH_3), 130.0, 132.5 (**C**H Tolyl), 133.5 (**C**-S Tolyl), 137.8 (**C**-CH_3 Tolyl), 155.8 (**C**=O).

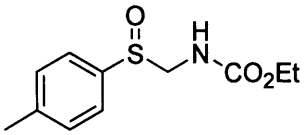
m/z (CI positive-methane): 102 (89), 125 (41), 133 (35), 135 (34), 137 (43), 225 (MH^+, 20%).

HRMS (CI positive-methane, Instrument Resolution 7000): Required: 226.09017. Found: 226.09038. Error: 0.93 ppm.

IR (υ_{max} cm^{-1}, DCM cast): 1032, 1251, 1300, 1537; 1690 (C=O); 2937; 3300 (N-H).

Melting Point: 68-69 °C.

Ethyl *N*-[(*p*-tolylsulfinyl)methyl]carbamate 156[174]



To a solution of carbamate **155** (5.00 g, 22.2 mmol) in a biphasic system DCM (75 mL) and saturated sodium bicarbonate aqueous solution (40 mL) at 0 °C, was slowly added *m*-CPBA 70-75 % (5.36 g, 21.7-23.3 mmol). The reaction mixture was stirred for 5 hours at room temperature and the two phases separated. The aqueous phase was extracted with DCM (30 mL), the combined organic phases were washed with saturated sodium bicarbonate aqueous solution (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica (EtOAc/PE 50/50 and MeOH/DCM 2/98) afforded carbamate **156** as a slightly yellow solid (4.41 g, 82% yield).

Rf: 0.30 (EtOAc/PE 40/60).

δ_H *(400 MHz, $CDCl_3$):* 1.22 (3H, t *J*=7.1; CH_2-C**H**$_3$), 2.40 (3H, s; C**H**$_3$ Tolyl), 4.10 overlapping (1H, dd *J*=13.1, 6.4; S-**H**CH-NH) and (2H, q *J*=7.1; C**H**$_2$-CH_3), 4.45 (1H, dd *J*=13.0, 7.4; S-HC**H**-NH), 6.43 (1H, br t *J*=6.5; N**H**), 7.33 (2H, dt *J*=7.9, 0.7; C**H** Tolyl), 7.53 (2H, d *J*=8.1; C**H** Tolyl).

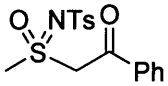
δ_C *(100 MHz, $CDCl_3$):* 14.4 (CH_2-**C**H_3), 21.4 (**C**H_3 Tosyl), 61.2 (**C**H_2-CH_3), 65.5 (**C**H_2-NH), 130.0, 135.4 (**C**H Tolyl), 137.8 (**C**-SO Tolyl), 142.0 (CH_3-**C** Tolyl), 156.0 (**C**=O).

m/z (DCI positive-isobutane): 102 (100), 124 (38), 125 (71), 141 (12), 242 (MH^+, 6%).

IR (υ_{max} cm^{-1}, DCM cast): 738, 801, 1066, 1094, 1238, 1445, 1491, 1514; 1713 (C=O); 3346 (N-H).

Melting Point: 91-92 °C.

***S*-Methyl-*S*-(2-oxo-2-phenylethyl)-*N*-tosylsulfoximine 160[201]**



To a solution of *S,S*-dimethyl-*N*-tosylsulfoximine **137** (0.50 g, 2.0 mmol) in a mixture of dry DMSO (1.5 mL)/THF (5.0 mL) at -78 °C under argon atmosphere was added dropwise LHMDS (4.0 mL, 1.0 M in THF, 4.0 mmol); the reaction mixture was allowed to warm up and was stirred for 1 hour before being cooled to -78 °C for the dropwise addition of benzoyl chloride (281 μL, 2.4 mmol). The reaction mixture was stirred 16 hours at room temperature then saturated ammonium chloride aqueous solution (5 mL) was added slowly followed by water (20 mL). The reaction mixture was extracted with DCM (3x50 mL), the combined organic phases were washed with water (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude material, ratio SM/Product 1:4 (^{1}H NMR), was purified by flash chromatography on silica (EtOAc/PE 20/80 and 40/60) to give sulfoximine **160** as a white solid in 51% yield (365 mg) along with some dialkylation product **160'**.

Rf: 0.30 (EtOAc/PE 40/60).

δ_H *(400 MHz, $CDCl_3$):* 2.38 (3H, s; C**H$_3$** Tosyl), 3.43 (3H, s; N(O)S-C**H$_3$**), 4.84 (1H, d *J*=15.3; N(O)S-**H**CH-C=O), 5.68 (1H, d *J*=15.3; N(O)S-HC**H**-C=O), 7.24 (2H, dd, *J*=8.0; *m*-C**H** Tosyl), 7.53 (2H, t *J*=8.0; *m*-C**H** Phenyl), 7.67 (1H, t *J*=7.5; *p*-C**H** Phenyl), 7.81 (2H, d *J*=8.3; *o*-C**H** Tosyl), 7.96 (2H, dd *J*=7.3, 1.2; *o*-C**H** Phenyl).

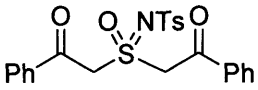
δ_C *(75 MHz, $CDCl_3$):* 21.6 (**C**H$_3$ Tosyl), 43.1 (N(O)S-**C**H$_3$), 60.8 (N(O)S-**C**H$_2$-C=O), 126.7, 126.6, 128.5, 129.4 (**C**H Aromatic), 140.0, 140.9 (**C** Aromatic), 143.2 (CH$_3$-**C** Tosyl), 198.5 (**C**=O).

m/z (CI positive-methane): 121 (65), 172 (20), 234 (20), 352 (MH^+, 100 %).

IR (υ_{max} cm^{-1}, DCM cast): 739, 974, 1078, 1150, 1286, 1597; 1686 (C=O), 2918.

Melting Point: 88-89 °C.

S,S-Bis(2-oxo-2-phenylethyl)-*N*-tosylsulfoximine **160'**



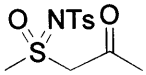
Rf: 0.30 (EtOAc/PE 20/80).

δ_H *(400 MHz, $CDCl_3$):* 2.39 (3H, s; C**H**$_3$ Tosyl), 5.52 (4H, s; 2xC**H**$_2$-C=O), 7.24 (2H, dd, *J*=8.1; *m*-C**H** Tosyl), 7.53 (4H, t *J*=7.5; *m*-C**H** Phenyl), 7.67 (2H, tt *J*=7.4, 1.1; *p*-C**H** Phenyl), 7.81 (2H, d *J*=8.3; *o*-C**H** Tosyl), 7.96 (4H, dd *J*=8.2, 1.0; *o*-C**H** Phenyl).

δ_C *(75 MHz, $CDCl_3$):* 21.6 (**C**H$_3$ Tosyl), 60.0 (N(O)S-**C**H$_2$-C=O), 126.6, 128.8, 129.1, 129.4, 135.0 (**C**H Aromatic), 135.2 (**C** Phenyl), 140.2, 143.2 (**C** Tosyl), 188.5 (**C**=O).

IR (υ_{max} cm^{-1}, DCM cast): 704, 739, 987, 1078, 1200, 1153, 1286, 1597; 1680 (C=O); 2991.

S-Methyl-S-(2-oxopropyl)-N-tosylsulfoximine 161[122]



To a solution of *S,S*-dimethyl-*N*-tosylsulfoximine **137** (1.00 g, 4 mmol) in dry DMSO (5 mL) at room temperature under argon atmosphere was added dropwise *n*-butyllithium (3.0 mL, 1.6 M in hexane, 5 mmol); the reaction mixture was stirred 45 minutes then dry acetonitrile (0.25 mL, 5 mmol) was added. The reaction mixture was stirred 16 hours at room temperature then poured into cold water (20 mL).The mixture was filtered through celite and the precipitate thus formed was washed with chloroform (3x30 mL). The aqueous phase was extracted with chloroform (2x30 mL), the combined organic phases were washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a thick yellow oil. The oil was dissolved in 4M hydrochloric acid (10 mL) and stirred 1 hour at room temperature before the white precipitate formed was filtered and washed with water (2x20 mL). Purification by recrystallisation from methanol gave sulfoximine **161** as a white powder (0.70 g, 60% yield).

Rf: 0.40 (EtOAc/PE 50/50).

δ_H (400 MHz, $CDCl_3$): 2.41 (3H, s; C**H**$_3$ Tosyl), 2.47 (3H, s; O=C-C**H**$_3$), 3.32 (3H, s; N(O)S-C**H**$_3$), 4.58 (1H, d *J*=14.8; N(O)S-**H**CH-C=O), 4.69 (1H, d *J*=14.7; N(O)S-HC**H**-C=O), 7.28 (2H, br d, *J*=8.6; C**H** Tosyl), 7.84 (2H, d *J*=8.5; C**H** Tosyl).

δ_C (100 MHz, $CDCl_3$): 21.5 (**C**H$_3$ Tosyl), 32.1 (O=C-**C**H$_3$), 42.7 (N(O)S-**C**H$_3$), 64.4 (N(O)S-**C**H$_2$-C=O), 126.6, 129.4 (**C**H Tosyl), 140.1 (**C**-SO$_2$ Tosyl), 143.3 (CH$_3$-**C** Tosyl), 196.4 (**C**=O).

m/z (CI positive-methane): 262 (29), 290 (MH^+, 100 %).

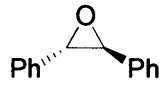
IR (υ_{max} cm^{-1}, DCM cast): 704, 897, 1053, 1146, 1280; 1722 (C=O); 2988, 3053.

Found: C 45.6, H 5.3, N 4.9. *Calculated for $C_{11}H_{15}NO_4S$:* C 45.7, H 5.2, N 4.8 %.

4.2.3. Cyclic sulfoximines

4.2.3.1. Derived from 5,6-diphenyl-1,4-oxathiane-2-one

(±)-*trans*-Stilbene oxide 166[174]



To a solution of *trans*-stilbene **165** (5.02 g, 27.7 mmol) in a biphasic system DCM (300 mL)/water (100 mL) at 0 °C, was added slowly *m*-CPBA 70-75 % (9.56 g, 38.8-41.6 mmol) followed by sodium hydrogenocarbonate (4.66 g, 55.4 mmol). The reaction mixture was stirred for 2 hours at room temperature and the two phases separated. The aqueous phase was extracted with DCM (150 mL), the combined organic phases were washed with saturated sodium bicarbonate aqueous solution (150 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Recrystallisation from methanol gave *trans*-stilbene oxide **166** as white crystals (4.33 g, 80 % yield).

Rf: 0.60 (ether/PE 10/90).

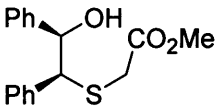
δ_H (300 MHz, $CDCl_3$): 3.87 (2H, s; **H**C-O-C**H**), 7.34-7.41 (10H, m; C**H** Phenyl).

δ_C (75 MHz, $CDCl_3$): 62.8 (H**C**-O-**C**H), 125.5, 128.3, 128.6 (**C**H Phenyl), 137.2 (**C** Phenyl).

m/z (ESI): 77 (31), 90 (100), 105 (34), 167 (63), 196 ($M^{\cdot+}$, 18%).

Melting Point: 68-69 °C (recrystallised from methanol, lit. 66-67 °C).

(±)-Methyl (4*RS*, 5*SR*)-5-hydroxy-4,5-diphenyl-3-thiapentanoate 167[173]



To a solution of sodium methoxide (54 mg, 1 mmol) and methylthioglycolate (0.66 mL, 7 mmol) in dry methanol (20 mL) under argon atmosphere, was added a solution of *trans*-stilbene oxide **166** (1.31 g, 7 mmol) in dry methanol (50 mL). The reaction mixture was heated under reflux for 2 hours then stirred 16 hours at room temperature. Water (150 mL) was added and the aqueous phase was extracted with ethyl acetate (2x150 mL), the combined organic phases were washed with brine (150 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (ether/PE 20/80 and 50/50) to give hydroxyester **167** as a white solid (1.80 g, 90 % yield).

Rf: 0.40 (ether/PE 50/50).

δ_H *(300 MHz, $CDCl_3$):* 2.37 (1H, d *J*=3.4; O**H**), 2.90 (1H, d *J*=15.2; S-**H**CH-C=O), 2.97 (1H, d *J*=15.2; S-HC**H**-C=O), 3.62 (3H, s; O**C**$\mathbf{H_3}$), 4.31 (1H, d *J*=6.8; Ph-C**H**-S), 5.03 (1H, dd *J*=6.9, 3.4; Ph-C**H**-OH), 7.23-7.33 (10H, m; C**H** Phenyl).

δ_C *(75 MHz, $CDCl_3$):* 32.8 (S-**C**$\mathbf{H_2}$-C=O), 52.3 (O**C**$\mathbf{H_3}$), 57.4 (Ph-**C**H-S), 76.6 (Ph-**C**H-OH), 126.8, 128.1, 128.4, 129.3 (*o-/m-***C**H Phenyl), 127.9, 128.1 (**C**H *p*-Phenyl), 137.6, 140.8 (**C** Phenyl), 170.7 (**C**=O).

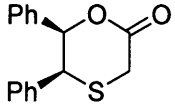
m/z (CI positive-methane): 91 (45), 181 (36), 197 (100), 285 (M(-OH)$^+$ 36 %).

IR (υ_{max} cm^{-1}, DCM cast): 1028, 1285, 1452, 1497, 1605; 1735 (C=O); 3034; 3500 (OH).

Found: C 67.8, H 6.1. *Calculated for $C_{17}H_{18}O_3S$:* C 67.5, H 6.0 %.

Melting Point: 50-52 °C. (recrystallised from ether/hexane, lit.[173] 44-46 °C)

(±)-*cis*-5,6-Diphenyl-1,4-oxathian-2-one 168[175]



Hydroxyester **167** (3.75 g, 12.40 mmol) and PTSA (23 mg, 0.12 mmol) were dissolved in dry benzene (100 mL, 0.1M) and heated under reflux for 2 days with Dean-Stark removal of water apparatus; then allowed to cool to room temperature and treated with water (100 mL). The reaction mixture was extracted with ethyl acetate (2x100 mL), the

combined organic phases were washed with saturated sodium bicarbonate aqueous solution (150 mL) and brine (150 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Recrystallisation from ethyl acetate/hexane gave lactone **168** as colourless crystals (2.27 g, 70 % yield).

Rf: 0.35 (ether/PE 30/70).

δ_H *(400 MHz, $CDCl_3$):* 3.52 (1H, d *J*=14.4; S-**H**CH-C=O), 3.99 (1H, d *J*=14.4; S-HC**H**-C=O), 4.55 (1H, d *J*=3.3; Ph-C**H**-O), 5.74 (1H, d *J*=3.3; Ph-C**H**-S), 6.94-6.99 (4H, m; C**H** Phenyl), 7.11-7.22 (6H, m; C**H** Phenyl).

δ_C *(75 MHz, $CDCl_3$):* 27.9 (S-**C**H_2-C=O), 49.4 (Ph-**C**H-S), 81.7 (Ph-**C**H-O), 126.3 (*o*-**C**H Phenyl C(5)), 127.9, 128.1, 128.0, 128.3 (**C**H Phenyl), 126.3 (*o*-**C**H Phenyl C(6)), 135.1 (**C** Phenyl C(6)), 136.0 (**C** Phenyl C(5)), 168.3 (**C**=O).

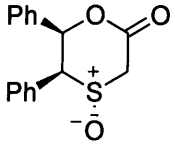
m/z (CI positive-methane): 271 (MH^+, 100 %).

IR (υ_{max} cm^{-1}, DCM cast): 739, 895, 1049, 1452; 1755 (C=O).

Found: C 70.9, H 5.2. *Calculated for $C_{16}H_{14}O_2S$:* C 71.1, H 5.2 %.

Melting Point: 146-147 °C (recrystallised from ethyl acetate/hexane).

(±)-(4*RS*, 5*RS*, 6*SR*)-5,6-Diphenyl-2-oxo-1,4-oxathiane 4-oxide 169[176]



To a solution of lactone **168** (1.00 g, 3.7 mmol) in a DCM/water 7/3 biphasic system (100 mL) cooled to 10 °C, was added slowly *m*-CPBA 70-75 % (0.96 g, 3.9-4.1 mmol) followed by sodium hydrogenocarbonate (0.62 g, 7.4 mmol). The reaction mixture was stirred 16 hours at room temperature, extracted with DCM (2x50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give sulfoxide **169** as white crystals (1.00 g, 95 % yield).

Rf: 0.30 (EtOAc/PE 40/60).

δ_H *(500 MHz, $CDCl_3$):* 3.70 (1H, d *J*=16.4; O=S-**H**CH-C=O), 4.09 (1H, d *J*=16.4; O=S-HC**H**-C=O), 4.37 (1H, d *J*=2.3; Ph-C**H**-O), 6.62 (1H, d *J*=2.3; Ph-C**H**-S=O), 7.05-7.08 (2H, m; C**H** Phenyl), 7.25-7.30 (8H, m; C**H** Phenyl).

δ_C (125 MHz, $CDCl_3$): 49.4 (O=S-**C**H_2-C=O), 66.9 (Ph-**C**H-O), 75.5 (Ph-**C**H-S=O), 126.0, 128.7, 129.3, 129.5 (*o-/m-***C**H Phenyl), 128.6, 129.2 (*p-***C**H Phenyl), 128.4 (**C** Phenyl C(5)), 134.9 (**C** Phenyl C(6)), 163.3 (**C**=O).

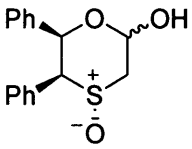
IR (υ_{max} cm^{-1}, DCM cast): 1055, 1225, 1452, 1499; 1747 (C=O); 3055.

m/z (CI positive-methane): 180 (100), 197 (55), 213 (35), 287 (MH^+, 18 %).

Found: C 67.2, H 4.9. *Calculated for $C_{16}H_{14}O_3S$:* C 67.1, H 4.9 %.

Melting Point: 148-149 °C (recrystallised from ethyl acetate).

(±)-(4*RS*, 5*RS*, 6*SR*)-2-Hydroxy-5,6-diphenyl-1,4-oxathiane 4-oxide 171



To a solution of sulfoxide **169** (500 mg, 1.75 mmol) in dry toluene (7 mL), under argon atmosphere at -78 °C, was added dropwise DIBAL (1.2 M in toluene, 2.9 mL, 3.50 mmol). Allowed to warm to room temperature, the mixture was stirred for 3 hours before 1M hydrochloric acid (2 mL) was added. The mixture was poured into DCM (50 mL) and hydrochloric acid 1M was added (50 mL), the resulting biphasic mixture was stirred vigorously for 30 minutes at room temperature. The aqueous phase was extracted with DCM (2x20 mL) and the combined organic phases were washed with brine (30 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude lactol (NMR ratio in $CDCl_3$ 1/0.8, in CD_3OD 1/0.5), was purified by recrystallisation from methanol to give the major isomer **171**M as a white solid (261 mg, 52% yield).

Rf: 0.15 (EtOAc/PE 40/60).

Major isomer **171**M

δ_H (400 MHz, $CDCl_3$): 2.75 (1H, dd *J*=14.1, 9.7; O=S-HC**H**$_{ax}$-CH), 2.99 (1H, ddd *J*=14.1, 1.7, 1.7; O=S-HC**H**$_{eq}$-CH), 3.86 (1H, d *J*=5.5; O**H**), 4.11 (1H, dd *J*=2.4, 1.6; O=S-C**H**$_{eq}$-Ph), 5.86 (1H, ddd *J*=9.6, 5.3, 1.5; C**H**$_{ax}$-OH), 6.04 (1H, d *J*=2.6; Ph-C**H**$_{ax}$-O), 7.05-7.08 (2H, m; C**H** Phenyl), 7.25-7.30 (8H, m; C**H** Phenyl).

δ_C (125 MHz, CD_3OD): 42.3 (**C**H_2), 60.6 (Ph-**C**H-S=O), 70.7 (Ph-**C**H-O), 89.0 (**C**H-OH), 127.6, 130.0, 130.5, 133.4 (*o-/m-***C**H Phenyl), 129.1, 130.3 (*p-***C**H Phenyl), 130.4, 140.9 (**C** Phenyl).

IR (υ_{max} cm^{-1}, DCM cast): 1035, 1130, 1302, 1447, 1495; 3228 (O-H).

Melting Point: 190 °C (recrystallised from methanol, decomposition).

Minor isomer **171**m

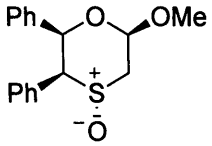
(peaks identified in a mixture of isomers)

δ_H (400 MHz, $CDCl_3$): 2.77 (1H, dd *J*=14.6, 3.3; O=S-HC**H**$_{ax}$-CH), 3.07 (1H, ddd *J*=14.6, 1.8, 1.8; O=S-**H**$_{eq}$CH-CH), 4.48 (1H, br s; O=S-C**H**$_{eq}$-Ph), 5.79 (1H, ddd *J*=10.5, 1.8, 1.6; O-C**H**$_{eq}$-OH), 6.40 (1H, d *J*=2.4; Ph-C**H**$_{ax}$-O), 6.97 (1H, d *J*=10.5; O**H**), 7.18-7.62 (10H, m; C**H** Phenyl).

Protection of the lactol by formation of the acetal

To a solution of the crude lactol **171** (48 mg, 0.17 mmol) in analar grade methanol (1 mL) was added PTSA (8 mg, 0.04 mmol) followed by trimethylorthoformate (136 µL, 1.25 mmol). The mixture was stirred for 48 hours at room temperature. Methanol was evaporated *in vacuo* and the crude oil purified by flash chromatography on silica (EtOAc/PE 30/70 to EtOAc 100%) to give a mixture of four products **172/173/172'/P** in a 1:0.7:0.3:0.2 ratio.

(±)-(2*RS*, 4*SR*, 5*SR*, 6*RS*)-5,6-Diphenyl-1,4-oxathian-2-methoxy 4-oxide **172**



Compound **172** was obtained in 14% yield (7 mg).

Rf: 0.25 (EtOAc/PE 30/70).

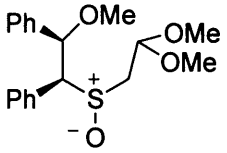
δ_H (400 MHz, 333 K, $CDCl_3$): 2.80 (1H, dd *J*=14.0, 9.6; O=S-HC**H**$_{ax}$-CH), 2.94 (1H, dd *J*=14.0, 1.7; O=S-HC**H**$_{eq}$-CH), 3.68 (3H, s; OC**H**$_3$), 4.11 (1H, d *J*=1.9; O=S-C**H**$_{eq}$-Ph), 5.45 (1H, dd *J*=9.6, 1.5; C**H**$_{ax}$-OMe), 6.02 (1H, d *J*=2.5; Ph-C**H**$_{ax}$-O), 7.14-7.26 (6H, m; *m-/p-*C**H** Phenyl), 7.48 (2H, m; *o-***C**H Phenyl C(6)), 7.57 (2H, m; *o-***C**H Phenyl C(5)).

δ_C (125 MHz, 333 K, $CDCl_3$): 42.9 (**C**H_2), 56.8 (O**C**H_3), 62.8 (O=S-**C**H-Ph), 71.2 (Ph-**C**H-O), 96.9 (**C**H-OMe), 125.6, 127.3, 128.2, 128.6, 131.0 (**C**H Phenyl), 130.5 (**C** Phenyl C(5)), 138.5 (**C** Phenyl C(6)).

m/z (CI positive-methane): 106 (100), 180 (15), 303 (MH^+, 14 %).

IR (υ_{max} cm^{-1}, DCM cast): 1045, 1130, 1369, 1452, 1497, 2851, 2931.

(±)-(3*RS*, 4*RS*)-1,1,5-Trimethoxy-4,5-diphenyl-3-thiapentane 3-oxide **173**



Compound **173** was obtained as the major side-product of the reaction described above (15% yield, 9 mg).

Rf: 0.25 (EtOAc/PE 40/60).

δ_H (400 MHz, $CDCl_3$): 2.37 (1H, dd *J*=13.2, 3.4; O=S-**H**CH-CH), 2.58 (1H, dd *J*=13.2, 8.2; O=S-HC**H**-CH), 3.12 (3H, s; Ph-CH-OC**H**$_3$), 3.21 (3H, s; C**H**$_3$O-CH-OMe), 3.29 (3H, s; MeO-CH-OC**H**$_3$), 3.78 (1H, d *J*=9.3; Ph-C**H**-S=O), 4.56 (1H, dd *J*=8.2, 3.4; MeO-C**H**-OMe), 4.90 (1H, d J=9.3; Ph-C**H**-O), 7.26-7.46 (10H, m; C**H** Phenyl).

δ_C (125 MHz, $CDCl_3$): 52.9 (**C**H_2), 53.2, 54.9 (H_3**C**O-CH-O**C**H_3), 57.2 (Ph-CH-O**C**H_3), 71.7 (Ph-**C**H-S=O), 82.6 (Ph-**C**H-O), 99.8 (MeO-**C**H-OMe), 127.9, 128.4, 128.5, 128.7, 130.1 (**C**H Phenyl), 131.6, 138.3 (**C** Phenyl).

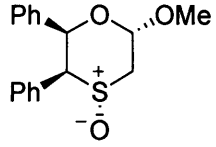
m/z (FAB positive-methane): 176 (100), 199 (47), 211 (71), 329 (73), 371 (MNa^+, 48%).

IR (υ_{max} cm^{-1}, DCM cast): 702, 1038, 1072, 1097, 1454, 1495, 2827, 2933.

Melting Point: 132-133 °C (recrystallised from ethyl acetate/hexane).

(±)-(2*SR*, 4*SR*, 5*SR*, 6*RS*)-5,6-diphenyl-2-methoxy-1,4-oxathiane 4-oxide **172'**

Peaks observed in a mixture of the two minors compounds:



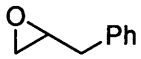
δ_H (500 MHz, $CDCl_3$): 2.87 (1H, dd *J*=14.9, 7.9; O=S-HC**H**$_{ax}$-CH), 3.05 (1H, dd *J*=15.0, 1.5; O=S-HC**H**$_{eq}$-CH), 3.52 (3H, s; OC**H**$_3$), 4.17 (1H, app. t *J*=2.2; Ph-C**H**$_{eq}$-S=O), 5.33 (1H, br

d J=4.1; C**H**$_{ax}$-OMe), 6.30 (1H, d J=2.2; Ph-C**H**$_{ax}$-O), 7.23-7.43 (8H, m; C**H** Phenyl), 7.54 (2H, m; C**H** Phenyl).

No information about the minor compound **P** could be extracted from analysis of mixtures of products.

4.2.3.2. Derived from 2-benzyl-1,4-oxathiane-2-one

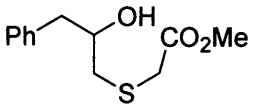
Benzyloxirane 176[202]



To a solution of allylbenzene **175** (56.1 mL, 0.42 mol) in DCM (800 mL) at 0 °C, was added *m*-CPBA (70-75%, 103.6 g, 0.42-0.45 mol) in small portions over 1 hour then stirred 1 hour from 0 to 10 °C. The mixture was cooled to 0 °C and the precipitated *m*-chlorobenzoic acid was filtered and washed with PE (100 mL). The filtrate was evaporated and the remaining *m*-chlorobenzoic acid was extracted twice by recrystallisation from PE. The organic phase was diluted with PE (300 mL) and washed with saturated sodium bicarbonate aqueous solution (3x150 mL) and brine (200 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude benzyloxirane **176** was obtained as a slightly yellow oil (51.9 g, 92% yield) and used without further purification.

Rf: 0.45 (ether/PE 5/95).
δ_H (400 MHz, $CDCl_3$): 2.57 (1H, dd J=5.0, 2.6; CH-**H**CH-Ph), 2.82 (1H, dd J=5.0, 4.1; CH-HC**H**-Ph), 2.84 (1H, dd J=14.6, 5.4; O-**H**CH-CH), 2.95 (1H, dd J=14.5, 5.7; O-HC**H**-CH), 3.15-3.20 (1H, dddd J=5.5, 5.4, 3.9, 2.7; CH_2-C**H**-CH_2), 7.25-7.36 (5H, m; C**H** Phenyl).
δc (100 MHz, $CDCl_3$): 38.8 (CH_2-**C**H-CH_2), 46.9 (O-**C**H_2-CH) 52.5 (CH-**C**H_2-Ph), 126.7 (*p*-**C**H Phenyl), 128.6, 129.0 (*o*-/*m*-**C**H Phenyl), 137.2 (**C** Phenyl).
m/z (ESI): 91 (100), 105 (34), 134 (MH^+, 38%).
IR (υ_{max} cm^{-1}, film, neat): 1259, 1454, 1496, 1584, 1605, 2918, 2991.

(±)-Methyl 6-phenyl-5-hydroxy-3-thiahexanoate 177[173]



To a solution of benzyloxirane **176** (51.9 g, 0.39 mol) and sodium methoxide (2.16 g, 0.04 mol) in analar grade methanol (1.0 L) was added slowly methyl thioglycolate (38.0 mL, 0.42 mmol); the reaction mixture was stirred for 16 hours at room temperature. Methanol was removed *in vacuo*, the resulting oil was diluted in ether (400 mL) and water (100 mL) was added. The aqueous phase was extracted with ether (2x100 mL), the combined organic phases were washed with water (2x150 mL) and brine (300 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford hydroxyester **177** as a slightly brown viscous oil (89.9 g, 96%) which was used without further purification.

Rf: 0.35 (EtOAc/PE 30/70).

δ_H *(400 MHz, $CDCl_3$):* 2.63 (1H, dd *J*=13.9, 8.2; S-**H**CH-CHOH), 2.83 (1H, dd *J*=14.0, 3.6; S-HC**H**-CHOH), 2.84 (2H, br d *J*=6.4; Ph-C**H$_2$**-CH), 3.26 (1H, d *J*=15.1; S-**H**CH-C=O), 3.31 (1H, d *J*=15.1; S-HC**H**-C=O), 3.71 (3H, s; OC**H$_3$**), 3.93-4.00 (1H, m; C**H**-OH), 7.21-7.32 (5H, m; C**H** Phenyl).

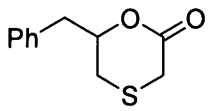
δ_C *(100 MHz, $CDCl_3$):* 33.9 (S-**C**H$_2$-C=O), 39.7 (S-**C**H$_2$-CHOH), 42.5 (Ph-**C**H$_2$-CH), 52.3 (O**C**H$_3$), 71.0 (**C**H-OH), 126.5 (*p*-**C**H Phenyl), 128.4, 129.3 (*o-/m*-**C**H Phenyl), 137.7 (**C** Phenyl), 171.3 (**C**=O).

m/z (FAB positive-Na): 175 (39), 176 (100), 179 (55), 199 (45), 263 (M+Na, 7%), 329 (35).

HRMS (CI positive-methane, Instrument Resolution 6000, Calculated for $C_{12}H_{16}O_3S+H^+$): Required: 241.08984. Found: 241.08937. Error 1.95 ppm.

IR (υ_{max} cm^{-1}, film, neat): 702, 746, 1082, 1132, 1280, 1495, 1583, 1603; 1736 (C=O); 2920; 3439 (O-H).

(±)-6-Benzyl-1,4-oxathian-2-one 178[175]



Hydroxyester **177** (30.00 g, 0.12 mol) and PTSA (0.24 g, 1.2 mmol) were dissolved in analar grade benzene (1.0 L) and heated under reflux for 15 days with Dean-Stark

removal of water apparatus; then allowed to cool to room temperature. Benzene was evaporated and the oily residue diluted in ethyl acetate (300 mL) then treated with water (100 mL). The aqueous phase was extracted with ethyl acetate (100 mL). The combined organic phases were washed with saturated sodium bicarbonate aqueous solution (150 mL) and brine (150 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Recrystallisation from ethyl acetate gave lactone **178** as a white solid (18.23 g, 73%).

Rf: 0.35 (EtOAc/PE 20/80).

δ_H *(400 MHz, $CDCl_3$):* 2.79 (1H, dd J=12.2, 11.1; S-HC**H**$_{ax}$-CH), 2.89 (1H, ddd J=12.3, 2.7, 0.5; S-HC**H**$_{eq}$-CH), 2.94 (1H, dd J=14.1, 6.7; Ph-**H**CH-CH), 3.19 (1H, dd J=13.9, 6.2; Ph-HC**H**-CH), 3.19 (1H, d J=14.8; S-HC**H**$_{ax}$-C=O) 3.52 (1H, dd J=14.8, 0.4; S-HC**H**$_{eq}$-C=O), 4.60-4.67 (1H, app. dtd J=11.0, 6.4, 2.7; CH_2-C**H**$_{ax}$-CH_2), 7.22-7.35 (5H, m; C**H** Phenyl).

δ_C *(100 MHz, $CDCl_3$):* 25.9 (Ph-**C**H_2-CH), 28.9 (S-**C**H_2-CH), 41.4 (S-**C**H_2-C=O), 79.9 (CH_2-**C**H-O), 127.2 (*p*-**C**H Phenyl), 128.8, 129.5 (*o-/m*-**C**H Phenyl), 135.4 (**C** Phenyl), 167.7 (C=O).

m/z (CI positive-methane): 91 (17), 117 (100), 209 (MH^+, 10%), 226 (9).

HRMS (CI positive-methane, Instrument Resolution 7000, Calculated for $C_{11}H_{12}O_2S+H^+$): Required: 209.06362. Found 209.06290. Error: 3.44 ppm.

Found: C 63.15, H 5.8. *Calculated for $C_{11}H_{12}O_2S$:* C 63.4, H 5.8 %.

IR (υ_{max} cm^{-1}, DCM cast): 702, 737, 1063, 1203, 1497; 1736 (C=O); 2920.

Melting Point: 86-88 °C (recrystallised from ethyl acetate).

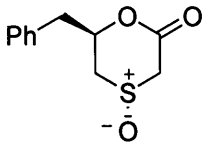
(±)-6-Benzyl-2-oxo-1,4-oxathiane 4-oxide 179[176]

To a solution of lactone **178** (17.7 g, 85 mmol) in a biphasic system of DCM (400 mL) and saturated sodium bicarbonate aqueous solution (200 mL) cooled to 0 °C, was added slowly *m*-CPBA 70-75% (21.0 g, 85-91 mmol). The reaction mixture was stirred for 3 hours from 0 °C to room temperature then the two phases were separated. The aqueous phase was extracted with DCM (2x100 mL), the combined organic phases were washed with saturated sodium bicarbonate aqueous solution (300 mL) and brine (300 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give sulfoxide as a mixture of two diastereoisomers *t*-**179** and *c*-**179** (*trans:cis* ratio=3:2) which were separated by flash chromatography on silica (EtOAc/PE 70/30 then EtOAc 100%).

t-**179**: 9.7 g, 51% yield.

c-**179**: 4.8 g, 25% yield.

(±)-(4*RS*, 6*RS*)-6-Benzyl-2-oxo-1,4-oxathiane 4-oxide *t*-**179**



Rf: 0.40 (EtOAc).

δ_H *(400 MHz, $CDCl_3$):* 2.67 (1H, dd *J*=14.2, 12.1; O=S-HC**H**$_{ax}$-CH), 3.01 (1H, dd *J*=14.0, 6.4; Ph-**H**CH-CH), 3.24 (1H, dd *J*=13.9, 6.2; Ph-HC**H**-CH), 3.60 (1H, d *J*=15.0; O=S-HC**H**$_{ax}$-C=O), 3.67 (1H, dd *J*=14.4, 2.7; O=S-HC**H**$_{eq}$-CH), 3.81 (1H, dd *J*=15.1, 0.7; O=S-HC**H**$_{eq}$-C=O), 4.23-4.49 (1H, app. dtd *J*=12.3, 6.3, 2.8; CH_2-C**H**$_{ax}$-CH_2), 7.23-7.35 (5H, m; C**H** Phenyl).

δ_C *(100 MHz, $CDCl_3$):* 41.1 (Ph-**C**H_2-CH), 50.0 (O=S-**C**H_2-CH), 54.2 (CH_2-**C**H-O), 75.5 (O=S-**C**H_2-CH), 127.6 (*p*-**C**H Phenyl), 129.0, 129.5 (*o-/m*-**C**H Phenyl), 134.8 (**C** Phenyl), 163.0 (**C**=O).

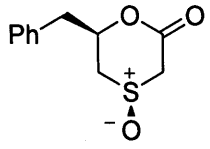
m/z (CI positive-methane): 117 (100), 225 (MH^+, 28%).

IR (υ_{max} cm^{-1}, KBr plate): 696, 729, 1060, 1110, 1454, 1499; 1744 (C=O); 2923.

Found: C 58.7, H 5.4. *Calculated for $C_{11}H_{12}O_3S$:* C 58.9, H 5.4 %.

Melting Point: 126-127 °C (recrystallised from ethyl acetate).

(±)-(4*RS*, 6*SR*)-6-Benzyl-2-oxo-1,4-oxathiane 4-oxide *c*-**179**



Rf: 0.25 (EtOAc).

δ_H *(400 MHz, $CDCl_3$):* 2.72 (1H, dd *J*=14.8, 11.2; O=S-HC**H**$_{ax}$-CH), 2.98 (1H, app dt *J*=14.8, 1.3; O=S-HC**H**$_{eq}$-CH), 3.07 (1H, dd *J*=14.2, 6.1; Ph-**H**CH-CH), 3.16 (1H, dd *J*=14.2, 6.3; Ph-HC**H**-CH), 3.46 (1H, dd *J*=15.9, 1.2; O=S-HC**H**$_{eq}$-C=O), 3.92 (1H, d *J*=16.0; O=S-HC**H**$_{ax}$-C=O), 5.32-5.38 (1H, app. dtd *J*=11.2, 6.1, 1.2; CH_2-C**H**$_{ax}$-CH_2), 7.23-7.34 (5H, m; C**H** Phenyl).

δ_C (100 MHz, $CDCl_3$): 40.4 (Ph-**C**H_2-CH), 49.8 (O=S-**C**H_2-CH), 50.0 (CH_2-**C**H-O), 72.6 (O=S-**C**H_2-CH), 127.3 (*p*-**C**H Phenyl), 128.7, 129.5 (*o-/m-***C**H Phenyl), 134.4 (**C** Phenyl), 163.3 (**C**=O).

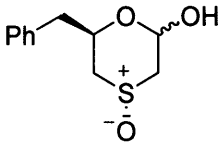
m/z (CI positive-methane): 85 (88), 117 (66), 149 (100), 167 (34), 225 (MH^+, 13%).

IR (υ_{max} cm^{-1}, KBr plate): 696, 729, 1061, 1111, 1501, 1454; 1732 (C=O); 2935, 2991.

Found: C 58.85, H 5.4. *Calculated for $C_{11}H_{12}O_3S$:* C 58.9, H 5.4 %.

Melting Point: 126-127 °C (recrystallised from ethyl acetate).

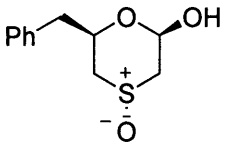
(±)-6-Benzyl-2-hydroxy-1,4-oxathiane 4-oxide *t*-180



To a solution of lactone *t*-**179** (2.00 g, 8.2 mmol) in dry toluene (60 mL), under argon atmosphere at -40 °C, was added dropwise DIBAL (1.2 M in toluene, 14.9 mL, 17.8 mmol). Allowed to warm to room temperature, the mixture was stirred for 16 hours before 0.5M Rochelle salt solution (80 mL) was added. The mixture was stirred 4 hours at room temperature until the two phases were well separated. The aqueous phase was extracted with ethyl acetate (3x50 mL), acidified to pH 5 and extracted again with ethyl acetate (2x50 mL); the combined organic phases were washed with brine (200 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The bulk of the major and more polar isomer *t*-**180**e was obtained as transparent crystals (1.03 g, 51% yield) by recrystallisation from ethyl acetate of the crude lactol. The filtrate was concentrated and purified by flash chromatography on silica (EtOAc/PE 80/20, EtOAc 100% then EtOAc/MeOH 98/2 and 94/6) to give both isomers *t*-**180**e, *t*-**180**a (0.25 g, 12% yield). Overall yield : 1.28 g, 63% yield. The ratio of isomers in the crude mixture is variable depending on the reaction.

(±)-(2*RS*, 4*RS*, 6*RS*)-6-Benzyl-2-hydroxy-1,4-oxathiane 4-oxide *t*-**180**e

(OH equatorial, major isomer)



Rf: 0.35 (EtOAc).

δ_H *(400 MHz, $CDCl_3$):* 2.34 (1H, ddd *J*=13.5, 11.2, 0.6; O=S-HC**H**$_{ax}$-$CHCH_2Ph$), 2.37 (1H, ddd *J*=13.2, 9.6, 0.7; O=S-HC**H**$_{ax}$-CHOH), 2.80 (1H, ddd *J*=14.2, 2.5, 1.7; O=S-HC**H**$_{eq}$-$CHCH_2Ph$), 2.86 (1H, dd *J*=13.9, 6.0; Ph-**H**CH-CH), 3.04 (1H, dd *J*=13.9, 7.3; Ph-HC**H**-CH), 3.10 (1H, ddd *J*=13.9, 2.4, 1.8; O=S-HC**H**$_{eq}$-CHOH), 3.32 (1H, d *J*= 5.3; O**H**), 4.74-4.79 (1H, dddd *J*=11.2, 7.1, 6.0, 1.7; CH_2-C**H**$_{ax}$-CH_2), 5.56 (1H, ddd *J*=9.4, 5.3, 1.7; C**H**$_{ax}$-OH), 7.21-7.33 (5H, m; C**H** Phenyl).

δ_C *(100 MHz, $CDCl_3$):* 41.6 (Ph-**C**H_2-CH), 47.5 (O=S-**C**H_2-$CHCH_2Ph$), 48.2 (O=S-**C**H_2-CHOH), 68.3 (CH_2-**C**H-CH_2), 89.0 (**C**H-OH), 126.9 (*p*-**C**H Phenyl), 128.6, 129.6 (*o-/m*-**C**H Phenyl), 136.4 (**C** Phenyl).

m/z (CI positive-methane): 91 (100), 105 (30), 118 (100), 209 (100), 227 (MH^+, 59%).

HRMS (CI positive-methane, Instrument Resolution 7000, Calculated for $C_{11}H_{14}O_3S+H^+$): Required: 227.07419. Found 227.07385. Error: 1.50 ppm.

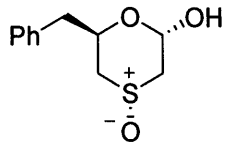
IR (υ_{max} cm^{-1}, KBr plate): 702, 750, 1034, 1126, 1331, 1456, 1493, 1603, 2874, 3196 (O-H).

Found: C 58.3, H 6.3. *Calculated for $C_{11}H_{14}O_3S$:* C 58.4, H 6.2 %.

Melting Point: 165-167 °C (recrystallised from ethyl acetate, partial decomposition).

(±)-(2*RS*, 4*SR*, 6*SR*)-6-Benzyl-2-hydroxy-1,4-oxathiane 4-oxide *t*-**180**a

(OH axial, minor isomer, peaks observed in a mixture of isomers)

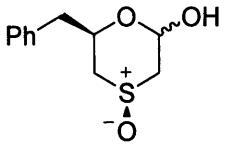


Rf: 0.45 (EtOAc).

δ_H *(400 MHz, $CDCl_3$):* 2.70 (1H, ddd *J*=14.2, 11.9, 0.8; O=S-HC**H**$_{ax}$-$CHCH_2Ph$), 3.02 (1H, dd *J*=14.0, 6.5; Ph-**H**CH-CH), 3.26 (1H, dd *J*=14.0, 6.3; Ph-HC**H**-CH), 3.50 (1H, br dd *J*=5.3, 2.0; C**H**$_{eq}$-OH), 3.60 (1H, ddd *J*=15.1, 0.3; O=S-HC**H**$_{eq}$-CHOH), 3.68 (1H, dd

J=14.3, 2.7; O=S-HC**H**$_{eq}$-CHCH$_2$Ph), 3.84 (1H, dd J=15.1, 0.9; O=S-HC**H**$_{ax}$-CHOH), 4.42-4.49 (1H, ddd J=12.2, 6.4, 2.7; CH$_2$-C**H**$_{ax}$-CH$_2$), 7.21-7.33 (5H, m; C**H** Phenyl).

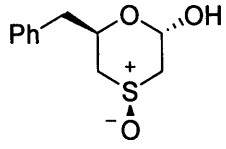
(±)-6-Benzyl-2-hydroxy-1,4-oxathiane 4-oxide *c*-180



To a solution of lactone *c*-**179** (1.00 g, 4.5 mmol) in dry toluene (30 mL), under argon atmosphere at -40 °C, was added dropwise DIBAL (1.2 M in toluene, 7.4 mL, 8.9 mmol). Allowed to warm to room temperature, the mixture was stirred for 24 hours before 0.5M Rochelle salt solution (80 mL) was added. The mixture was stirred 4 hours at room temperature until the two phases were separated. The aqueous phase was extracted with ethyl acetate (3x50 mL), acidified to pH 5 and extracted again with ethyl acetate (50 mL). The combined organic phases were washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give lactol (5') as a mixture of isomers. The bulk of the major isomer *c*-**180**a was obtained as transparent crystals by recrystallisation from ethyl acetate of the crude product (0.226 g, 22% yield). The filtrate was concentrated and purified by chromatography on silica (EtOAc/PE 80/20, EtOAc 100% then EtOAc/MeOH 94/6) to give both isomers *c*-**180**a, *c*-**180**e (0.217 g, 21% yield). Overall yield: 0.443 g, 44%. The ratio of isomers in the crude mixture is variable depending on the reaction.

(±)-(2*RS*, 4*RS*, 6*SR*)-6-Benzyl-2-hydroxy-1,4-oxathiane 4-oxide *c*-**180**a

(OH axial, recrystallised material, major isomer)



Rf: 0.40 (EtOAc/MeOH 96/4).

δ_H *(500 MHz, CDCl$_3$):* 2.47 (1H, dd J=12.1, 11.7; O=S-HC**H**$_{ax}$-CHCH$_2$Ph), 2.56 (1H, app dt J=11.9, 2.6; O=S-HC**H**$_{ax}$-CHOH), 2.80 (1H, dd J=13.7, 6.6; Ph-**H**CH-CH), 2.97 (1H, dd J=13.7, 6.6; Ph-HC**H**-CH), 3.35 (1H, ddd J=12.1, 1.6, 0.7; O=S-HC**H**$_{eq}$-CHCH$_2$Ph), 3.51 (1H, dd J=11.7, 2.3; O=S-HC**H**$_{eq}$-CHOH), 3.81 (1H, dd J=3.6, 2.4; O**H**), 4.33-4.38 (1H,

app. dtd *J*=11.5, 6.6, 1.6; CH_2-C**H**$_{ax}$-CH_2), 5.54 (1H, dt *J*=3.6, 2.7; C**H**$_{eq}$-OH), 7.20-7.35 (5H, m; C**H** Phenyl).

δ_C (125 MHz, $CDCl_3$): 41.7 (Ph-**C**H_2-CH), 54.7 (O=S-**C**H_2-CHOH), 55.6 (O=S-**C**H_2-CHCH_2Ph), 65.8 (CH_2-**C**H-CH_2), 92.0 (**C**H-OH), 127.0 (*p*-**C**H Phenyl), 128.6, 129.5 (*o*-/*m*-**C**H Phenyl), 136.3 (**C** Phenyl).

m/z (CI positive-methane): 91 (98), 117 (100), 135 (99), 209 (91), 227 (MH^+, 79%), 255 (25).

HRMS (CI positive-methane, Instrument Resolution 7000, Calculated for $C_{11}H_{14}O_3S+H^+$): Required: 227.07419. Found 227.07429. Error: 0.44 ppm.

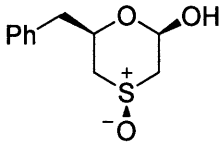
IR (υ_{max} cm^{-1}, KBr plate): 700, 739, 1016, 1115, 1308, 1493, 1605, 2906, 3036; 3298 (O-H).

Found: C 58.2, H 6.5. *Calculated for $C_{11}H_{14}O_3S$:* C 58.4, H 6.2 %.

Melting Point: 162-165 °C (recrystallised from ethyl acetate, partial decomposition).

(±)-(2*RS*, 4*SR*, 6*RS*)-6-Benzyl-2-hydroxy-1,4-oxathiane 4-oxide *c*-**180**e

(OH equatorial, minor isomer, peaks observed in the mixture of isomers)

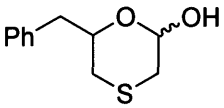


Rf: 0.50 (EtOAc/MeOH 96/4).

δ_H (400 MHz, $CDCl_3$): 2.42 (1H, dd *J*=12.1, 11.4; O=S-HC**H**$_{ax}$-CHCH_2Ph), 2.60 (1H, dd *J*=11.6, 9.8; O=S-HC**H**$_{ax}$-CHOH), 2.83 (1H, dd *J*=13.7, 7.2; Ph-**H**CH-CH), 3.11 (1H, dd *J*=13.9, 6.2; Ph-HC**H**-CH), 3.25 (1H, ddd *J*=12.1, 2.5, 1.3; O=S-HC**H**$_{eq}$-CHCH_2Ph), 3.53 (1H, ddd *J*=11.6, 2.5, 1.5; O=S-HC**H**$_{eq}$-CHOH), 3.64-3.70 (1H, app. dtd *J*=11.3, 7.1, 1.0; CH_2-C**H**$_{ax}$-CH_2), 4.73 (1H, dd *J*=9.8, 2.5; C**H**$_{ax}$-OH), 6.26 (1H, d *J*=5.9; O**H**), 7.20-7.35 (5H, m; C**H** Phenyl).

δ_C (100 MHz, $CDCl_3$): 41.3 (Ph-**C**H_2-CH), 53.1 (O=S-**C**H_2-CHOH), 55.4 (O=S-**C**H_2-CHCH_2Ph), 69.0 (CH_2-**C**H-CH_2), 91.2 (**C**H-OH), 126.9 (*p*-**C**H Phenyl), 128.5, 129.3 (*o*-/*m*-**C**H Phenyl), 135.8 (**C** Phenyl).

(±)-6-Benzyl-1,4-oxathian-2-ol 185



To a solution of lactone **178** (18.2 g, 87 mmol) in dry toluene (180 mL), under argon atmosphere at -78 °C, was added dropwise DIBAL (1.2 M in toluene, 80.2 mL, 96 mmol). The mixture was stirred for 1 hour at -78 °C before acetic acid solution (11.0 mL, AcOH/H_2O 1/1 v/v) was added carefully. The aluminium salts formed were filtered and washed with ethyl acetate (3x100 mL); the combined organic phases were washed with brine (150 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude lactol **185** was obtained as a mixture of isomers **185**e/**185**a (16.8 g, 91% yield, ratio 1:0.6 in $CDCl_3$) used without further purification for the next step.

Rf: 0.30 (EtOAc/PE 25/75).

(±)-(2*RS*, 6*RS*)-6-Benzyl-1,4-oxathian-2-ol **185**e

δ_H *(500 MHz, $CDCl_3$):* 2.21 (1H, ddd *J*=13.4, 1.9, 1.6; S-HC**H**$_{eq}$-$CHCH_2Ph$), 2.46 (1H, dd *J*=13.5, 10.4; S-HC**H**$_{ax}$-$CHCH_2Ph$), 2.49 (1H, ddd *J*=13.0, 2.6, 1.5; S-HC**H**$_{eq}$-CHOH), 2.55 (1H, dd *J*=13.6, 8.6 Hz S-HC**H**$_{ax}$-CHOH), 2.75 (1H, dd *J*=13.7, 6.7; Ph-**H**CH-CH), 2.96 (1H, dd *J*=13.7, 6.7; Ph-HC**H**-CH), 3.40 (1H, d *J*=5.4; O**H**), 3.98-4.07 (1H, ddd *J*=10.4, 6.7, 1.9; CH_2-C**H**-CH_2), 4.85 (1H, ddd, C**H**$_{ax}$-OH), 7.18-7.31 (5H, m; Phenyl).

δ_C *(125 MHz, $CDCl_3$):* 29.6 (S-**C**H_2-$CHCH_2Ph$), 31.1 (S-**C**H_2-CHOH), 42.5 (**C**H_2Ph), 79.9 (CH_2-**C**H-CH_2), 95.9 (O-**C**H-OH), 126.5 (*p*-**C**H Phenyl), 128.4, 129.3 (*o*-/*m*-**C**H Phenyl), 137.2 (**C** Phenyl).

(±)-(2*RS*, 6*SR*)-6-Benzyl-1,4-oxathian-2-ol **185**a

δ_H *(500 MHz, $CDCl_3$):* 2.25 (1H, dd *J*=13.5, 2.2; S-HC**H**$_{eq}$-$CHCH_2Ph$), 2.43 (1H, ddd *J*=13.5, 2.3, 0.9; S-HC**H**$_{eq}$-CHOH), 2.56 (1H, dd *J*=13.5, 10.9; S-HC**H**$_{ax}$-$CHCH_2Ph$), 2.67 (1H, dd *J*=13.7, 7.3; Ph-**H**CH-CH), 2.89 (1H, dd *J*=13.7, 6.2; Ph-HC**H**-CH), 3.02 (1H, dd *J*=13.5, 2.2; S-HC**H**$_{ax}$-CHOH), 4.07 (1H, d *J*=9.1; O**H**), 4.33-4.39 (1H, dddd *J*=10.8, 7.7, 6.2, 2.1; CH_2-C**H**-CH_2), 5.24 (1H, d *J*=8.9; C**H**$_{eq}$-OH), 7.18-7.31 (5H, m; C**H** Phenyl).

δ_C (125 MHz, $CDCl_3$): 30.5 (S-**C**H_2-$CHCH_2Ph$), 32.5 (S-**C**H_2-CHOH), 42.3 (**C**H_2Ph), 69.2 (CH_2-**C**H-CH_2), 88.0 (O-**C**H-OH), 126.5 (*p*-**C**H Phenyl), 128.4, 129.3 (*o-/m-***C**H Phenyl), 137.0 (**C** Phenyl).

HRMS (FAB positive-Na, Instrument Resolution 7000, Calculated for $C_{11}H_{14}O_2S$+Na): Required: 233.06122. Found: 233.06068. Error 2.32 ppm.

IR (υ_{max} cm^{-1}, film, neat): 980, 1039, 1122, 1454, 1497, 2918; 3389 (O-H).

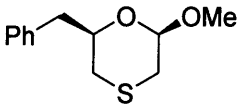
Melting Point: 77-81 °C (crystallised mixture of isomers).

(±)-6-Benzyl-2-methoxy-1,4-oxathiane 186[177]

To a solution of the crude lactol **185** (16.8 g, 80 mmol, ratio 1:0.6) in analar grade methanol (320 mL) was added PTSA (1.5 g, 8 mmol) followed by trimethylorthoformate (87 mL, 0.80 mol). The mixture was stirred for 16 hours at room temperature. Methanol was evaporated *in vacuo* and the crude oil purified by flash chromatography on silica (EtOAc/PE 10/90). The product **186** was obtained as a mixture of two isomers **186**e/**186**a (12.01 g, 67% yield, ratio 1:0.65) which were not separated.

For the analyses; the two isomers of a fraction of the above mentioned mixture were separated by flash chromatography on silica.

(±)-(2*RS*, 6*RS*)-6-Benzyl-2-methoxy-1,4-oxathiane **186**e



Rf: 0.45 (EtOAc/PE 10/90).

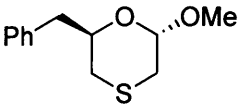
δ_H (400 MHz, $CDCl_3$): 2.24 (1H, dd *J*=13.4, 1.7; S-HC**H**$_{eq}$-$CHCH_2Ph$), 2.44 (1H, app. dt *J*=13.0, 1.7; S-HC**H**$_{eq}$-CHOMe), 2.51 (1H, dd *J*=13.4, 10.5; S-HC**H**$_{ax}$-$CHCH_2Ph$), 2.60 (1H, dd *J*=13.0, 9.1; S-HC**H**$_{ax}$-CHOMe), 2.77 (1H, dd *J*=13.7, 5.9; Ph-**H**CH-CH), 2.98 (1H, dd *J*=13.7, 7.4; Ph-HC**H**-CH), 3.37 (3H, s; OC**H**$_3$), 3.92-3.98 (1H, dddd *J*=10.5, 7.4, 6.0, 1.9; CH_2-C**H**$_{ax}$-CH_2), 4.48 (1H, dd *J*=9.0, 1.9; C**H**$_{ax}$-OMe), 7.20-7.32 (5H, m; C**H** Phenyl).

δ_C (100 MHz, $CDCl_3$): 29.8 (S-**C**H_2-CHOMe), 30.1 (S-**C**H_2-$CHCH_2Ph$), 42.4 (**C**H_2Ph), 55.7 (O**C**H_3), 76.7 (CH_2-**C**H-CH_2), 102.5 (O-**C**H-OMe), 126.4 (*p*-**C**H Phenyl), 128.3, 129.4 (*o-/m-***C**H Phenyl), 137.5 (**C** Phenyl).

IR (υ_{max} cm^{-1}, film, neat): 700, 754; 1067 (C-O); 1495, 1454, 2833, 2918.

Found: C 64.6, H 7.3. *Calculated for $C_{12}H_{16}O_2S$:* C 64.3, H 7.2 %.

(±)-(2*RS*, 6*SR*)-6-Benzyl-2-methoxy-1,4-oxathiane **186**a



Rf: 0.35 (EtOAc/PE 10/90).

δ_H (400 MHz, $CDCl_3$): 2.33 (1H, ddd *J*=13.4, 3.1, 1.7; Ph-**H**CH-CH), 2.43 (1H, dd *J*=13.6, 1.8; S-HC**H**$_{eq}$-CHOMe), 2.65 (1H, dd *J*=13.4, 10.6; Ph-HC**H**-CH), 2.71 (1H, dd *J*=13.6, 6.0; S-HC**H**$_{eq}$-CHCH$_2$Ph), 2.82 (1H, dd *J*=13.6, 7.8; S-HC**H**$_{ax}$-CHCH$_2$Ph), 2.97 (1H, dd *J*=13.7, 2.9; S-HC**H**$_{ax}$-CHOMe), 3.18 (3H, s; OC**H**$_3$), 4.22-4.29 (1H, dddd *J*=10.5, 7.8, 5.9, 2.0; CH$_2$-C**H**$_{ax}$-CH$_2$), 4.75 (1H, m; C**H**$_{eq}$-OMe), 7.19-7.33 (5H, m; C**H** Phenyl).

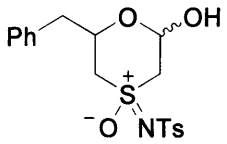
δ_C (100 MHz, $CDCl_3$): 29.5 (S-**C**H$_2$-CHCH$_2$Ph), 30.3 (S-**C**H$_2$-CHOMe), 42.3 (**C**H$_2$Ph), 54.8 (O**C**H$_3$), 69.5 (CH$_2$-**C**H-CH$_2$), 95.6 (O-**C**H-OMe), 126.4 (*p*-**C**H Phenyl), 128.2, 129.4 (*o*-/*m*-**C**H Phenyl), 137.6 (**C** Phenyl).

IR (υ_{max} cm^{-1}, film, neat): 700, 756; 1047 (C-O); 1454, 1495, 2831, 2918.

*m/z (FAB positive-Na, **186**):* 163 (24), 164 (47), 193 (100), 222 (24), 224 (26), 247 (M+Na, 52%).

HRMS (FAB positive-Na, Instrument Resolution 7000, Calculated for $C^{12}H^{16}O^2S$+Na): Required: 247.07687. Found: 247.07742. Error 2.23 ppm.

(±)-6-Benzyl-2-hydroxy-4-[*N*-(*p*-tolylsulfonyl)imino]-1,4-oxathiane 4-oxide 181[182]



In a round bottom flask fit with a condenser, a solution of acetal (*c*-**184**e/*t*-**184**e ratio 1:0.7) (2.60 g, 6.34 mmol) in glacial acetic acid (22 mL) was heated to 85 °C; when dissolution was complete, triflic acid (4.44 mmol, 1M solution in water) was added and the mixture heated under reflux for 4 days. The reaction was cooled to room temperature and saturated sodium bicarbonate aqueous solution was added slowly until no more gas was formed. The aqueous phase was extracted with DCM (2x50 mL), the combined organic phases were washed with saturated sodium bicarbonate aqueous solution (3x50 mL), dried over magnesium sulfate, filtered and concentrated to give lactol as a mixture of 4

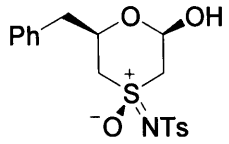
diastereomers (2.36 g, 94% yield). Lactols *c*-**181**e/*t*-**181**e/*t*-**181**a were obtained in a 1:0.6:0.3 ratio and only traces of *c*-**181**a were observed.

Upon the same treatment acetal *c*-**184**a (1.27 g, 3.10 mmol) was converted to the corresponding lactol, obtained as an inseparable mixture of isomers *c*-**181**e/*c*-**181**a in 96% yield (1.17 g, ratio 1/0.4).

Rf: 0.25 (EtOAc/PE 40/60).

Major isomers, OH equatorial.

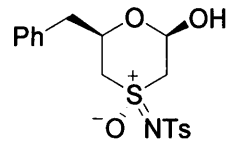
(±)-(2*RS*, 4*SR*, 6*RS*)-6-Benzyl-2-hydroxy-4-[*N*-(*p*-tolylsulfonyl)imino]-1,4-oxathiane 4-oxide *c*-**181**e



δ_H *(400 MHz, $CDCl_3$):* 2.40 (3H, s; C**H**$_3$), 2.82 (1H, dd *J*=13.7, 10.8; N(O)S-HC**H**$_{ax}$-$CHCH_2Ph$), 2.92 (1H, dd *J*=14.2, 5.8; Ph-HC**H**-CH), 2.95 (1H, dd *J*=13.4, 8.9; N(O)S-HC**H**$_{ax}$-CHOH), 3.05 (1H, dd *J*=14.1, 7.0; Ph-**H**CH-CH), 3.77 (1H, ddd *J*=13.6, 3.3, 1.7; N(O)S-HC**H**$_{eq}$-$CHCH_2Ph$), 4.08 (1H, ddd *J*=13.4, 3.4, 1.9; N(O)S-HC**H**$_{eq}$-CHOH), 4.23 (1H, d *J*=5.4; O**H**), 4.25-4.31 (1H, dddd *J*=10.7, 7.3, 5.5, 1.7; CH_2-C**H**$_{ax}$-CH_2), 5.27 (1H, ddd *J*=8.8, 5.3, 1.9; C**H**$_{ax}$-OH), 7.20-7.32 (7H, C**H** Aromatic), 7.80-7.83 (2H, m; C**H** Tosyl).

δ_C *(125 MHz, $CDCl_3$):* 21.5 (**C**H_3), 40.7 (**C**H_2-Ph), 54.8 (N(O)S-**C**H_2-$CHCH_2Ph$), 56.6 (N(O)S-**C**H_2-CHOH), 71.7 (CH_2-**C**H-CH_2), 93.0 (O-**C**H-OH), 126.6, 127.3, 128.7, 129.4, 129.6 (**C**H Aromatic), 135.1 (**C** Phenyl), 140.0 (**C**-SO_2 Tosyl), 143.4 (CH_3-**C** Tosyl).

(±)-(2*RS*, 4*RS*, 6*RS*)-6-Benzyl-2-hydroxy-4-[*N*-(*p*-tolylsulfonyl)imino]-1,4-oxathiane 4-oxide *t*-**181**e



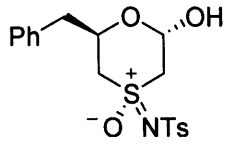
δ_H *(400 MHz, $CDCl_3$):* 2.41 (3H, s; C**H**$_3$), 2.89 (1H, *J*=14.1, 6.4; Ph-HC**H**-CH), 3.09 (1H, *J*=14.1, 6.4; Ph-**H**CH-CH), 3.10 (1H, ddd *J*=14.1, 11.2, 0.6; N(O)S-HC**H**$_{ax}$-$CHCH_2Ph$), 3.23

(1H, ddd *J*=13.8, 9.4, 0.6; N(O)S-HC**H**$_{ax}$-CHOH), 3.44 (1H, ddd *J*=14.1, 3.4, 1.8; N(O)S-HC**H**$_{eq}$-CHCH$_2$Ph), 3.86 (1H, ddd *J*=13.8, 3.4, 2.0; N(O)S-HC**H**$_{eq}$-CHOH), 4.17-4.25 (1H, app. dtd *J*=11.3, 6.4, 1.8; CH$_2$-C**H**$_{ax}$-CH$_2$), 4.32 (1H, br s; O**H**), 5.19 (1H, dd *J*=9.4, 2.0; C**H**$_{ax}$-OH), 7.16 (2H, d *J*=7.2; *m*-C**H** Tosyl), 7.25-7.32 (5H, m; C**H** Phenyl), 7.82 (2H, d *J*=7.2; *o*-C**H** Tosyl).

δ_C (125 MHz, CDCl$_3$): 21.5 (**C**H$_3$), 40.8 (**C**H$_2$-Ph), 53.4 (N(O)S-**C**H$_2$-CHCH$_2$Ph), 57.0 (N(O)S-**C**H$_2$-CHOH), 71.0 (CH$_2$-**C**H-CH$_2$), 91.9 (**C**H-OH), [126.5-129.5] (**C**H Aromatic), 134.9 (**C** Phenyl), 139.9 (**C**-SO$_2$ Tosyl), 143.3 (CH$_3$-**C** Tosyl).

Minor isomers, OH axial.

(±)-(2*RS*, 4*SR*, 6*SR*)-6-Benzyl-2-hydroxy-4-[*N*-(*p*-tolylsulfonyl)imino]-1,4-oxathiane 4-oxide *t*-**181**a

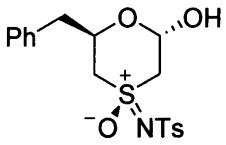


δ_H (400 MHz, CDCl$_3$): 2.41 (3H, s; C**H$_3$**), 2.89 (1H, dd *J*=14.1, 6.6; Ph-HC**H**-CH), 3.06 (1H, dd *J*=14.1, 6.6; Ph-**H**CH-CH), 3.23 (1H, dd *J*=14.3, 11.3; N(O)S-HC**H**$_{ax}$-CH-CH$_2$Ph), 3.51 (1H, dd *J*=14.4, 3.7; N(O)S-HC**H**$_{ax}$-CHOH), 3.44 (1H, ddd *J*=14.3, 3.4, 1.9; N(O)S-HC**H**$_{eq}$-CHCH$_2$Ph), 3.86 (1H, ddd *J*=14.4, 3.4, 1.9; N(O)S-HC**H**$_{eq}$-CHOH), 4.75-4.84 (1H, app. dtd *J*=11.5, 6.6, 1.7; CH$_2$-C**H**$_{ax}$-CH$_2$), 4.90 (1H, br s; O**H**), 5.65 (1H, dd *J*=3.7, 1.9; C**H**$_{eq}$-OH), 7.18 (2H, d *J*=7.2; *m*-C**H** Tosyl), 7.25-7.32 (5H, m; C**H** Phenyl), 7.80 (2H, d *J*=7.2; *o*-C**H** Tosyl).

δ_C (125 MHz, CDCl$_3$): 21.5 (**C**H$_3$), 40.5 (**C**H$_2$-Ph), 54.6 (N(O)S-**C**H$_2$-CHCH$_2$Ph), 55.7 (N(O)S-**C**H$_2$-CHOH), 65.3 (CH$_2$-**C**H-CH$_2$), 90.0 (**C**H-OH), [126.5, 129.5] (**C**H Aromatic), 134.9 (**C** Phenyl), 139.9 (**C**-SO$_2$ Tosyl), 143.3 (CH$_3$-**C** Tosyl).

*m/z (CI positive-methane, c-**181**e/t-**181**e/t-**181**a):* 117 (100), 155 (63), 172 (71), 350 (15), 378 (25), 396 (MH$^+$, 13%).

(±)-(2*RS*, 4*RS*, 6*SR*)-6-Benzyl-2-hydroxy-4-[*N*-(*p*-tolylsulfonyl)imino]-1,4-oxathiane 4-oxide *c*-**181**a



δ_H *(400 MHz, $CDCl_3$):* 2.41 (3H, s; C**H**$_3$), 3.05 (1H, dd *J*=14.4, 6.3; Ph-HC**H**-CH), 3.17 (1H, dd *J*=14.0, 3.8; N(O)S-HC**H**$_{ax}$-CHOH), 3.78 (1H, ddd *J*=14.0, 3.7, 1.7; N(O)S-HC**H**$_{eq}$-CHOH), 4.04 (1H, ddd *J*=13.5, 3.4, 1.6; N(O)S-HC**H**$_{eq}$-CHCH$_2$Ph), 4.84-4.89 (1H, dddd *J*=11.0, 7.3, 5.9, 1.4; CH$_2$-C**H**$_{ax}$-CH$_2$), 5.39 (1H, d *J*=9.0; O**H**), 5.64 (1H, ddd *J*=9.0, 3.9, 1.5; C**H**$_{ax}$-OH), 7.20-7.32 (7H, C**H** Aromatic), 7.80-7.83 (2H, m; C**H** Tosyl).

Other protons overlap with other isomer.

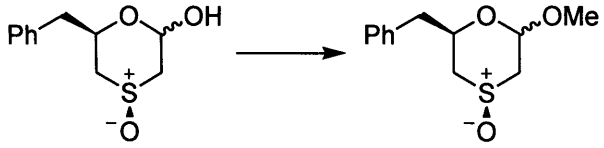
δ_C *(125 MHz, $CDCl_3$):* 21.6 (**C**H$_3$), 40.6 (**C**H$_2$-Ph), 53.7 (N(O)S-**C**H$_2$-CHOH), 56.4 (N(O)S-**C**H$_2$-CHCH$_2$Ph), 67.4 (CH$_2$-**C**H-CH$_2$), 90.0 (**C**H-OH), 126.7, 127.3, 128.7, 129.5, 129.6 (**C**H Aromatic), 134.9 (**C** Phenyl), 139.7 (**C**-SO$_2$ Tosyl), 143.6 (CH$_3$-**C** Tosyl).

*m/z (FAB positive-methane, c-**181**e/c-**181**a):* 154 (100), 220 (18), 289 (21), 307 (50), 396 (MH^+, 7%).

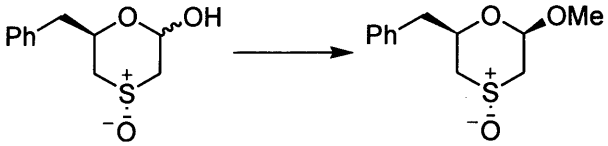
IR (υ_{max} cm^{-1}, DCM cast): 818, 1047, 1217, 1149, 1306, 1454, 1597, 2922, 2976; 3352 (OH).

(±)-6-Benzyl-2-methoxy-1,4-oxathiane 4-oxide 183[176]

*By protection of the corresponding lactols c-**180** and t-**180**:*

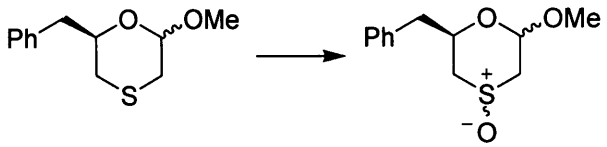


To a solution of the crude lactol *c*-**180** (242 mg, 1.1 mmol) in analar grade methanol (5 mL) was added PTSA (20 mg, 0.1 mmol) followed by trimethyl orthoformate (1.17 mL, 10.7 mmol). The mixture was stirred for 72 hours at room temperature. Methanol was evaporated *in vacuo* and the crude oil purified by flash chromatography on silica gel (EtOAc/PE 30/70 to EtOAc 100%) to give acetal *c*-**183** in 56% yield (257 mg) as a mixture of 2 isomers *c*-**183**e/*c*-**183**a in a 2:1 ratio.



To a solution of the crude lactol *t*-**180** (300 mg, 1.33 mmol) in analar grade methanol (10 mL) was added PTSA (25 mg, 0.13 mmol) followed by trimethyl orthoformate (728 μL, 6.65 mmol). The mixture was stirred for 48 hours at room temperature. Methanol was evaporated *in vacuo* and the crude oil purified by flash chromatography on silica gel (EtOAc/PE 30/70 to EtOAc 100%) to give product as single isomer *t*-**183**e in 70% yield (224 mg).

By oxidation of the mixture of the corresponding sulfides ***186:***

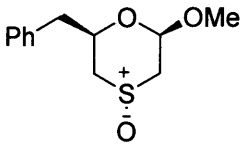


To a solution of acetal **186** (12.01 g, 53.5 mmol, ratio 1:0.65) in DCM (270 mL) and saturated sodium bicarbonate aqueous solution (90 mL) was added slowly *m*-CPBA 70-75% (13.21 g, 53.6-57.5 mmol). The reaction mixture was stirred for 2 hours at room temperature before the two phases were separated. The aqueous phase was extracted with DCM (2x50 mL), the combined organic phases were washed with saturated sodium bicarbonate aqueous solution (2x150 mL) and brine (200 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give sulfoxide **183** as a mixture of four diastereomers *t*-**183**e/*c*-**183**a/*c*-**183**e/*t*-**183**a in a 1:0.6:0.6:0.2 NMR ratio. The crude material was purified by flash chromatography on silica (EtOAc, MeOH/DCM 5/95) to give a first fraction with isomers *t*-**183**e/*c*-**183**a/*c*-**183**e (11.41 g, 89%) and a second fraction which gave after recrystallisation from ethyl acetate sulfoxide *t*-**183**a (0.78 g, 6%); overall yield 95%. The corresponding sulfones were obtained in variable yields (up to 22%) depending on the reaction.

Rf(t-**183**e/*c*-**183**a/*c*-**183**e*):* 0.35 (EtOAc).

Rf(t-**183a***):* 0.10 (EtOAc).

(±)-(2*RS*, 4*RS*, 6*RS*)-6-Benzyl-2-methoxy-1,4-oxathiane 4-oxide *t*-**183**e



δ_H *(500 MHz, $CDCl_3$):* 2.37 (1H, ddd *J*=14.1, 11.2, 0.6; O=S-HC**H**$_{ax}$-$CHCH_2Ph$), 2.40 (1H, ddd *J*=13.8, 9.6, 0.6; O=S-HC**H**$_{ax}$-CHOMe), 2.81 (1H, ddd *J*=14.0, 2.4, 1.5; O=S-HC**H**$_{eq}$-$CHCH_2Ph$), 2.86 (1H, dd *J*=13.8, 5.6; Ph-**H**CH-CH), 3.02 (1H, ddd *J*=13.8, 2.4, 1.7; O=S-HC**H**$_{eq}$-CHOMe), 3.05 (1H, dd *J*=13.9, 7.8; Ph-HC**H**-CH), 3.41 (3H, s; OC**H**$_3$), 4.68-4.72 (1H, dddd *J*=11.2, 7.7, 5.6, 1.5; CH_2-C**H**$_{ax}$-CH_2), 5.09 (1H, dd *J*=9.5, 1.7; C**H**$_{ax}$-OMe), 7.22-7.31 (5m; C**H** Phenyl).

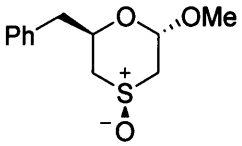
δ_C *(125 MHz, $CDCl_3$):* 41.5 (**C**H_2-Ph), 47.6 (O=S-**C**H_2-$CHCH_2Ph$), 48.0 (S-**C**H_2-CHOMe), 56.4 (O**C**H_3), 68.2 (CH_2-**C**H-CH_2), 95.5 (O-**C**H-OMe), 126.8 (*p*-**C**H Phenyl), 126.8, 128.4 (*o*-/*m*-**C**H Phenyl), 136.6 (**C** Phenyl).

m/z (FAB positive-methane): 183 (21), 209 (100), 241 (MH^+, 90%).

IR (υ_{max} cm^{-1}, DCM cast): 1045, 1134, 1454, 1494, 1600, 2839, 2933.

Melting Point: 53-54 °C (slow crystallisation of the pure oil upon standing at room temperature).

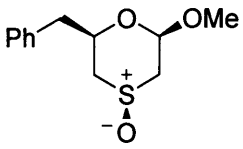
(±)-(2*RS*, 4*RS*, 6*SR*)-6-Benzyl-2-methoxy-1,4-oxathiane 4-oxide *c*-**183**a



δ_H *(400 MHz, $CDCl_3$):* 2.56 (1H, dd *J*=13.4, 3.9; O=S-HC**H**$_{ax}$-$CHCH_2Ph$), 2.65 (1H, dd *J*=13.6, 1.8; O=S-HC**H**$_{ax}$-CHOMe), 2.84 (1H, dd *J*=13.4, 10.6; Ph-**H**CH-CH), 2.99 (1H, dd *J*=13.6, 6.0; Ph-HC**H**-CH), 3.08 (3H, s; OC**H**$_3$), 3.41 (1H, dd *J*=13.6, 7.8; O=S-HC**H**$_{eq}$-$CHCH_2Ph$), 3.54 (1H, dd *J*=13.7, 2.9; O=S-HC**H**$_{eq}$-CHOMe), 4.02-4.09 (1H, dddd *J*=11.4, 7.4, 5.8, 1.5; CH_2-C**H**$_{ax}$-CH_2), 5.03 (1H, dd J=2.7, 2.3; C**H**$_{eq}$-OMe), 7.19-7.33 (5H, m; C**H** Phenyl).

δ_C *(100 MHz, $CDCl_3$):* 41.7 (**C**H_2Ph), 54.3 (O=S-**C**H_2-CHOMe), 55.1 (O**C**H_3), 55.6 (O=S-**C**H_2-$CHCH_2Ph$), 65.9 (CH_2-**C**H-CH_2), 98.2 (O-**C**H-OMe), 126.9 (*p*-**C**H Phenyl), 128.5, 129.4 (*o*-/*m*-**C**H Phenyl), 136.4 (**C** Phenyl).

(±)-(2*RS*, 4*SR*, 6*RS*)-6-Benzyl-2-methoxy-1,4-oxathiane 4-oxide *c*-**183**e

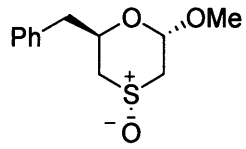


δ_H *(400 MHz, $CDCl_3$):* 2.51 (1H, app t *J*=11.8; O=S-HC**H**$_{ax}$-$CHCH_2Ph$), 2.61 (1H, dd *J*=11.6, 9.9; O=S-HC**H**$_{ax}$-CHOMe), 2.87 (1H, dd *J*=13.6, 6.0; Ph-**H**CH-CH), 3.10 (1H, dd *J*=13.9, 7.3; Ph-HC**H**-CH), 3.36 (1H, ddd *J*=12.1, 2.5, 1.3; O=S-HC**H**$_{eq}$-$CHCH_2Ph$), 3.42 (3H, s; O**C**H_3), 3.57 (1H, ddd *J*=11.6, 2.3, 1.3; O=S-HC**H**$_{eq}$-CHOMe), 3.62-3.69 (1H, dddd *J*=11.3, 7.1, 5.7, 1.3; CH_2-C**H**$_{ax}$-CH_2), 4.33 (1H, dd J=9.9, 1.5; C**H**$_{ax}$-OMe), 7.21-7.32 (5H, m; C**H** Phenyl).

δ_C *(100 MHz, $CDCl_3$):* 41.4 (**C**H_2Ph), 54.4 (O=S-**C**H_2-CHOMe), 54.8 (O=S-**C**H_2-$CHCH_2Ph$), 56.7 (O**C**H_3), 69.3 (CH_2-**C**H-CH_2), 97.6 (O-**C**H-OMe), 126.9 (*p*-**C**H Phenyl), 128.4, 129.1 (*o*-/*m*-**C**H Phenyl), 136.2 (**C** Phenyl).

*m/z (FAB positive-methane, c-**183**a/ c-**183**e):* 154 (88), 209 (45), 241 (100%, MH).

(±)-(2*RS*, 4*SR*, 6*SR*)-6-Benzyl-2-methoxy-1,4-oxathiane 4-oxide *t*-**183**a



δ_H *(500 MHz, $CDCl_3$):* 2.56 (1H, dd *J*=14.8, 4.3, 0.6; O=S-HC**H**$_{ax}$-CHOMe), 2.59 (1H, ddd *J*=14.1, 11.1, 0.5; O=S-HC**H**$_{ax}$-$CHCH_2Ph$), 2.84 (1H, dd *J*=13.7, 5.0; Ph-**H**CH-CH), 2.90 (1H, ddd *J*=14.0, 2.7, 1.5; O=S-HC**H**$_{eq}$-$CHCH_2Ph$), 2.90 (1H, dd *J*=13.8, 8.3; Ph-HC**H**-CH), 3.05 (1H, ddd *J*=14.8, 2.6, 1.3; O=S-HC**H**$_{eq}$-CHOMe), 3.07 (3H, s; O**C**H_3), 4.89-4.93 (1H, ddddd *J*=11.1, 8.3, 5.0, 1.5, 0.6; H_2C-C**H**$_{ax}$-CH_2), 4.94 (1H, br d J=3.9; O-C**H**$_{eq}$-OMe), 7.20-7.29 (5H, m; C**H** Phenyl).

δ_C *(125 MHz, $CDCl_3$):* 41.6 (**C**H_2Ph), 45.5 (S-**C**H_2-CHOMe), 48.2 (S-**C**H_2-$CHCH_2Ph$), 55.7 (O**C**H_3), 58.1 (CH_2-**C**H-CH_2), 96.5 (O-**C**H-OMe), 126.6 (*p*-**C**H Phenyl), 128.3, 129.6 (*o*-/*m*-**C**H Phenyl), 136.9 (**C** Phenyl).

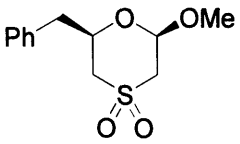
m/z (CI positive-methane): 91 (76), 105 (29), 117 (99), 183 (25), 209 (100), 241 (55%, MH^+), 269 (59).

HRMS (CI positive-methane, Instrument Resolution 6000, Calculated for $C_{12}H_{16}O_3S+H^+$): Required: 241.08984. Found: 241.08980. Error 0.17 ppm.

IR (υ_{max} cm^{-1}, DCM cast): 702, 743, 1043, 1123, 1454, 1496, 1603, 2835, 2920.

Melting Point: 95-96 °C (recrystallised from ethyl acetate).

(±)-(2*RS*, 6*RS*)-6-Benzyl-2-methoxy-1,4-oxathiane 4,4-dioxide



Rf: 0.40 (EtOAc/PE 25/75).

δ_H (500 MHz, $CDCl_3$): 2.84 (1H, dd *J*=13.9, 11.1, 0.6; O_2S-HC**H**$_{ax}$-$CHCH_2Ph$), 2.88 (1H, dd *J*=13.6, 5.9; Ph-**H**CH-CH), 2.96 (1H, ddd *J*=13.6, 9.5, 0.5; O_2S-HC**H**$_{ax}$-CHOMe), 2.98 (1H, ddd *J*=13.9, 3.4, 1.9; O_2S-HC**H**$_{eq}$-$CHCH_2Ph$), 3.07 (1H, dd *J*=13.8, 7.4; Ph-HC**H**-CH), 3.26 (1H, ddd *J*=13.5, 3.3, 1.9; O_2S-HC**H**$_{eq}$-CHOMe), 3.43 (3H, s; OC**H**$_3$), 4.07-4.12 (1H, dddd *J*=11.0, 7.6, 5.8, 2.0; CH_2-C**H**$_{ax}$-CH_2), 4.70 (1H, dd J=9.4, 1.9; C**H**$_{ax}$-OMe), 7.20-7.34 (5H, m; C**H** Phenyl).

δ_C (100 MHz, $CDCl_3$): 41.1 (**C**H_2Ph), 55.3 (O_2S-**C**H_2-$CHCH_2Ph$), 56.2 (O_2S-**C**H_2-CHOMe), 57.0 (O**C**H_3), 71.8 (CH_2-**C**H-CH_2), 99.6 (O-**C**H-OMe), 127.2 (*p*-**C**H Phenyl), 128.7, 129.4 (*o*-/*m*-**C**H Phenyl), 135.7 (**C** Phenyl).

m/z (CI positive-methane): 91 (96), 117 (100), 165 (84), 224 (40), 225 (100), 226 (56), 255 (30), 257 (20%, MH^+).

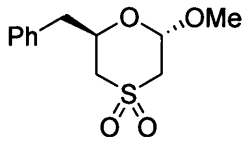
HRMS (CI positive-methane, Instrument Resolution 7000, Calculated for $C_{12}H_{16}O_4S+H^+$): Required: 257.08475. Found 257.08496. Error: 0.82 ppm.

IR (υ_{max} cm^{-1}, film, neat): 702, 743, 1117, 1138; 1319 (SO_2); 1456, 2841, 2928.

Found: C 56.2, H 6.3. *Calculated for $C_{12}H_{16}O_4S$:* C 56.2, H 6.3 %.

Melting Point: 135-138 °C (recrystallised from ethyl acetate).

(±)-(2*RS*, 6*SR*)-6-Benzyl-2-methoxy-1,4-oxathiane 4,4-dioxide



Rf: 0.35 (EtOAc/PE 25/75).

δ_H *(400 MHz, $CDCl_3$):* 2.86 (1H, dd *J*=13.7, 5.2; Ph-**H**CH-CH), 2.95 (1H, dd *J*=13.7, 8.0; Ph-HC**H**-CH), 2.99 (1H, dd *J*=13.9, 11.1; O_2S-HC$\mathbf{H_{ax}}$-$CHCH_2Ph$), 3.09 (3H, s; O$\mathbf{CH_3}$), 3.10 (1H, ddd *J*=13.7, 2.9, 1.8; O_2S-HC$\mathbf{H_{eq}}$-$CHCH_2Ph$), 3.19 (1H, dd *J*=14.3, 3.9; O_2S-HC$\mathbf{H_{ax}}$-CHOMe), 3.25 (1H, ddd *J*=14.2, 2.9, 1.8; O_2S-HC$\mathbf{H_{eq}}$-CHOMe), 4.57-4.63 (1H, dddd *J*=11.1, 7.1, 5.2, 1.9; CH_2-C$\mathbf{H_{ax}}$-CH_2), 5.07 (1H, dd J=3.8, 1.7; C$\mathbf{H_{eq}}$-OMe), 7.20-7.33 (5H, m; C**H** Phenyl).

δ_C *(100 MHz, $CDCl_3$):* 41.2 (**C**H_2Ph), 54.1 (S-**C**H_2-CHOMe), 55.7 (O**C**H_3), 56.7 (S-**C**H_2-$CHCH_2Ph$), 67.8 (CH_2-**C**H-CH_2), 96.9 (O-**C**H-OMe), 127.0 (*p*-**C**H Phenyl), 128.4, 129.4 (*o-/m*-**C**H Phenyl), 135.9 (**C** Phenyl).

m/z (CI positive-methane): 91 (52), 117 (100), 165 (54), 225 (100), 255 (20%, MH^+).

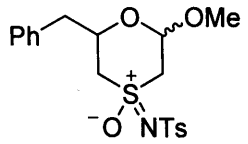
HRMS (CI positive-methane, Instrument Resolution 7000, Calculated for $C_{12}H_{16}O_4S+H^+$): Required: 257.08475. Found 257.08517. Error: 1.63 ppm.

IR (υ_{max} cm^{-1}, film, neat): 702, 743, 1117, 1138; 1319 (SO_2); 1456, 2841, 2928.

Found: C 56.2, H 6.3. *Calculated for $C_{12}H_{16}O_4S$:* C 56.2, H 6.3 %.

Melting Point: 136-140 °C (recrystallised from ethyl acetate).

(±)-6-Benzyl-2-methoxy-4-[*N*-(*p*-tolylsulfonyl)imino]-1,4-oxathiane 4-oxide 184

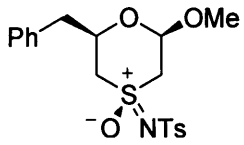


To a solution of acetals *t*-**183**e/*c*-**183**a/*c*-**183**e (3.11 g, 12.9 mmol, ratio 1:0.8:0.2) and copper(II) triflate (0.47 g, 1.3 mmol) in dry acetonitrile (75 mL) under argon atmosphere, was added [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane (5.31 g, 14.2 mmol) in small fractions over 1 hour, and the mixture was stirred for 3 days at room temperature before acetonitrile was evaporated *in vacuo*. The crude material, containing the desired product as a mixture of 3 diastereomers *c*-**184**e/*t*-**184**e/*c*-**184**a (ratio 1:0.8:0.3), was purified by

flash chromatography on silica (EtOAc/PE 25/75 and 50/50) to give sulfoximines distributed between 2 fractions; a mixture of two isomers *c*-**184**e/*t*-**184**e (4.18 g, 79% yield) was obtained as the first fraction, followed by isomer *c*-**184**a (0.53 g, 10%) in the second fraction; overall yield 89 %.

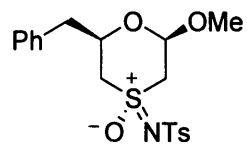
Rf(c-**184**e/*t*-**184**e*):* 0.35 (EtOAc/PE 25/75).
Rf(c-**184**a*):* 0.20 (EtOAc/PE 30/70).

(±)-(2*RS*, 4*SR*, 6*RS*)-6-Benzyl-2-methoxy-4-[*N*-(*p*-tolylsulfonyl)imino]-1,4-oxathiane 4-oxide *c*-**184**e



δ_H *(400 MHz, $CDCl_3$):* 2.40 (3H, s; C**H**$_3$ Tosyl), 2.86 (1H, dd *J*=13.6, 10.7; N(O)S-HC**H**$_{ax}$-$CHCH_2Ph$), 2.93 (1H, dd *J*=13.3, 9.0; N(O)S-HC**H**$_{ax}$-CHOMe), 2.95 (1H, dd *J*=14.1, 5.1; Ph-**H**CH-CH), 3.04 (1H, dd *J*=14.1, 7.6; Ph-HC**H**-CH), 3.42 (3H, s; OC**H**$_3$), 3.87 (1H, ddd *J*=13.7, 3.2, 1.7; N(O)S-HC**H**$_{eq}$-$CHCH_2Ph$), 4.04 (1H, ddd *J*=13.3, 3.2, 1.8; N(O)S-HC**H**$_{eq}$-CHOMe), 4.21-4.27 (1H, dddd *J*=10.9, 7.7, 5.2, 1.8; CH_2-C**H**$_{ax}$-CH_2), 4.80 (1H, dd *J*=8.9, 1.9; C**H**$_{ax}$-OMe), 7.22-7.35 (7H, m; C**H** Aromatic), 7.82 (2H d *J*=8.3; C**H** Tosyl).
δ_C *(100 MHz, $CDCl_3$):* 21.5 (**C**H_3 Tosyl), 40.7 (**C**H_2-Ph), 55.4 (N(O)S-**C**H_2-$CHCH_2Ph$), 55.8 (N(O)S-**C**H_2-CHOMe), 57.1 (O**C**H_3), 71.6 (CH_2-**C**H-CH_2), 99.2 (O-**C**H-OMe), 126.6 (**C**H Tosyl), 127.2 (*p*-**C**H Phenyl), 128.6, 129.4 (*o-/m*-**C**H Phenyl), 129.5 (**C**H Tosyl), 135.2 (**C** Phenyl), 140.2 (**C**-SO_2 Tosyl), 143.2 (CH_3-**C** Tosyl).

(±)-(2*RS*, 4*RS*, 6*RS*)-6-Benzyl-2-methoxy-4-[N-(*p*-tolylsulfonyl)imino]-1,4-oxathiane 4-oxide *t*-**184**e



δ_H *(500 MHz, $CDCl_3$):* 2.40 (3H, s; C**H**$_3$ Tosyl), 2.90 (1H, dd *J*=14.0, 5.8; Ph-**H**CH-CH), 3.08 (1H, dd *J*=14.0, 7.3; Ph-HC**H**-CH), 3.11 (1H, dd *J*=14.1, 11.4; N(O)S-HC**H**$_{ax}$-$CHCH_2Ph$), 3.18 (1H, dd *J*=13.8, 9.5; N(O)S-HC**H**$_{ax}$-CHOMe), 3.43 (3H, s; OC**H**$_3$), 3.55 (1H,

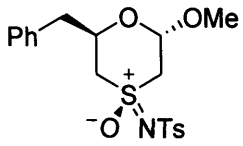
ddd *J*=14.2, 3.3, 1.7; N(O)S-HC**H**$_{eq}$-CHCH$_2$Ph), 3.80 (1H, ddd *J*=13.9, 3.3, 1.9; N(O)S-HC**H**$_{eq}$-CHOMe), 4.13-4.18 (1H, dddd *J*=11.4, 7.3, 5.6, 1.7; CH$_2$-C**H**$_{ax}$-CH$_2$), 4.73 (1H, dd *J*=9.5, 1.8; C**H**$_{ax}$-OMe), 7.19 (2H, br dt *J*=6.8, 1.6; C**H** Tosyl), 7.25-7.33 (5H, m; C**H** Phenyl), 7.83 (2H br dt *J*=8.3, 1.7; C**H** Tosyl).

δ$_C$ *(125 MHz, CDCl$_3$):* 21.5 (**C**H$_3$ Tosyl), 40.8 (**C**H$_2$-Ph), 55.7 (N(O)S-**C**H$_2$-CHCH$_2$Ph), 56.1 (N(O)S-**C**H$_2$-CHOMe), 57.0 (O**C**H$_3$), 71.0 (CH$_2$-**C**H-CH$_2$), 98.2 (O-**C**H-OMe), 126.6 (**C**H Tosyl), 127.3 (*p*-**C**H Phenyl), 128.7, 129.4 (*o-/m*-**C**H Phenyl), 129.3 (**C**H Tosyl), 135.1 (**C** Phenyl), 140.2 (**C**-SO$_2$ Tosyl), 143.2 (CH$_3$-**C** Tosyl).

m/z (FAB positive-methane): 154 (100), 289 (12), 307 (25), 410 (MH$^+$, 18%).

Melting Point: 144-145 °C.

(±)-(2*RS*, 4*RS*, 6*SR*)-6-Benzyl-2-methoxy-4-[*N*-(*p*-tolylsulfonyl)imino]-1,4-oxathiane 4-oxide *c*-**184**a



δ$_H$ *(500 MHz, CDCl$_3$):* 2.40 (3H, s; C**H**$_3$ Tosyl), 2.87 (1H, dd *J*=13.9, 5.0; Ph-**H**CH-CH), 2.92 (1H, dd *J*=14.0, 7.7; Ph-HC**H**-CH), 2.94 (1H, dd *J*=13.6, 11.0; N(O)S-HC**H**$_{ax}$-CHCH$_2$Ph), 3.07 (3H, s; OC**H**$_3$), 3.24 (1H, dd *J*=14.2, 4.1; N(O)S-HC**H**$_{ax}$-CHOMe), 3.72 (1H, ddd *J*=13.6, 3.1, 1.6; N(O)S-HC**H**$_{eq}$-CHCH$_2$Ph), 4.36 (1H, ddd *J*=14.2, 3.2, 1.5; N(O)S-HC**H**$_{eq}$-CHOMe), 4.58-4.63 (1H, dddd *J*=10.9, 7.7, 4.9, 1.4; CH$_2$-C**H**$_{ax}$-CH$_2$), 5.10 (1H, br dd *J*=3.9, 1.3; C**H**$_{eq}$-OMe), 7.19-7.32 (7H, m; C**H** Aromatic), 7.84 (2H, d *J*=8.3; C**H** Tosyl).

δ$_C$ *(100 MHz, CDCl$_3$):* 21.1 (**C**H$_3$ Tosyl), 40.4 (**C**H$_2$-Ph), 53.4 (N(O)S-**C**H$_2$-CHCH$_2$Ph), 55.2 (O**C**H$_3$), 56.5 (N(O)S-**C**H$_2$-CHOMe), 67.1 (CH$_2$-**C**H-CH$_2$), 96.2 (O-**C**H-OMe), 126.2 (**C**H Aromatic), 126.7 (*p*-**C**H Phenyl), 128.1, 128.7, 129.2 (**C**H Aromatic), 135.5 (**C** Phenyl), 140.7 (**C**-SO$_2$ Tosyl), 142.8 (CH$_3$-**C** Tosyl).

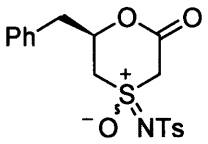
m/z (FAB positive-Na): 173 (53), 176 (100), 177 (15), 199 (28), 326 (13), 432 (M+Na, 13%).

IR (υ_{max} *cm^{-1}, DCM cast):* 729, 985, 1045, 1226, 1126, 1151; 1319 (SO$_2$); 1454, 1495, 1600, 2932, 3057.

Found: C 55.7, H 5.8. N 3.2. *Calculated for C$_{19}$H$_{23}$NO$_5$S$_2$:* C 55.7, H 5.7, N 3.4 %.

Melting Point: 153-154 °C (recrystallised from ethyl acetate).

6-Benzyl-2-oxo-4-[*N*-(*p*-tolylsulfonyl)imino]-1,4-oxathiane 4-oxide 174



To a solution of lactol **181** (0.50 g, 1.26 mmol) in dry DCM (5.0 mL) under argon atmosphere was added at once DMP (1.07 g, 2.53 mmol) and the mixture was stirred 1 hour at room temperature. The excess of DMP was then filtered and washed once with DCM (20 mL) and saturated sodium sulfite aqueous solution (20 mL) was added to the filtrate. The product was extracted with DCM (2x20 mL), the combined organic phases were washed with saturated sodium sulfite aqueous solution (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give crude material. Separation by flash chromatography on silica (EtOAc/PE 40/60) gave the corresponding lactone as 2 diastereomers **174**M (69 mg) and **174**m (28 mg) in 20% overall yield.

Major isomer **174**M

Rf: 0.45 (EtOAc/PE 40/60).

δ_H *(400 MHz, Acetone-d6):* 2.40 (3H, s; CH_3), 3.22 (1H, dd *J*=14.4, 6.9; Ph-**H**CH-CH), 3.26 (1H, dd *J*=14.3, 5.7; Ph-HC**H**-CH), 3.82 (1H, dd *J*=14.4, 11.6; N(O)S-HC$\mathbf{H}_{ax}$-CH), 4.35 (1H, dd *J*=14.3, 2.4; N(O)S-HC$\mathbf{H}_{eq}$-CH), 4.64 (1H, br d *J*=15.8; N(O)S-**H**CH-C=O), 5.14 (1H, br d *J*=15.7; N(O)S-HC**H**-C=O), 5.30-5.37 (1H, dddd *J*=11.6, 6.7, 5.8, 2.4; CH_2-C$\mathbf{H}_{ax}$-CH_2), 7.26-7.36 (7H, m; C**H** Aromatics), 7.77 (2H, br d *J*=8.5; C**H** Tosyl).

δ_C *(100 MHz, Acetone-d6):* 21.3 (**C**H_3), 40.1 (**C**H_2-Ph), 56.6 (N(O)S-**C**H_2-CH), 57.1 (N(O)S-**C**H_2-C=O), 76.4 (CH_2-**C**H-CH_2), 127.3 (*p*-**C**H Phenyl), 128.1, 128.3, 128.6, 128.8, 129.4, 130.2, 130.6 (**C**H Aromatic), 135.9 (**C** Phenyl), 141.6 (**C**-SO_2 Tosyl), 144.0 (CH_3-**C** Tosyl), 161.3 (**C**=O).

IR (υ_{max} cm^{-1}, *DCM cast):* 1072, 1150, 1224, 1454, 1496, 1599; 1732 (C=O); 2928.

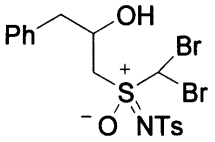
Melting Point: 160-161 °C (recrystallised from ethyl acetate).

Minor isomer **174**m

Rf: 0.35 (EtOAc/PE 40/60).

δ_H *(500 MHz, Acetone-d6):* 2.40 (3H, s; CH_3), 3.22 (1H, dd *J*=14.3, 7.2; Ph-**H**CH-CH), 3.26 (1H, dd *J*=14.2, 5.3; Ph-HC**H**-CH), 4.03 (1H, d *J*=14.5; N(O)S-**H**CH-CH), 4.07 (1H, d *J*=14.3; N(O)S-HC**H**-CH), 4.90 (1H, br d *J*=15.3; N(O)S-**H**CH-C=O), 4.97 (1H, br d *J*=15.6; N(O)S-HC**H**-C=O), 5.45-5.50 (1H, ddd *J*=10.6, 7.2, 5.1; CH_2-C**H**-CH_2), 7.25-7.35 (7H, m; C**H** Aromatic), 7.75 (2H, br d *J*=8.5; C**H** Tosyl).

S-Dibromomethyl-S-[(2-hydroxy-3-phenyl)propyl]-N-(p-tolylsulfonyl) sulfoximine 187



To a suspension of lactols *c*-**181**e/*t*-**181**e/*t*-**181**a (1.20 g, 3.0 mmol, ratio 1:0.6:0.3) in aqueous dioxane (48 mL, dioxane/water 1:3) was added barium carbonate (1.81 g, 9.2 mmol). Bromine (0.55 mL, 10.7 mmol) was slowly added with vigorous stirring and the reaction mixture was stirred for 3 hours at room temperature. When the reaction showed completion, saturated sodium sulfite aqueous solution was added until the mixture was decolourised. The product was extracted with DCM (3x50 mL), the combined organic phases were washed with saturated sodium sulfite aqueous solution (1x50 mL) and brine (1x100 mL), dried over magnesium sulfate and concentrated. Purification by flash chromatography on silica (EtOAc/PE 20/80) afforded **187** as two diastereomers (0.80 g, 67% yield).

Major isomer **187**M

Rf: 0.45 (EtOAc/PE 20/80).

δ_H *(500 MHz, $CDCl_3$):* 2.42 (3H, s; C**H**$_3$), 2.77 (1H, d *J*=3.4; O**H**), 2.89 (1H, dd *J*=13.9, 7.8; Ph-**H**CH-CHOH), 2.94 (1H, dd *J*=13.7, 5.4; Ph-HC**H**-CHOH), 3.83 (1H, dd *J*=14.4, 2.2; N(O)S-**H**CH-CHOH), 3.97 (1H, dd *J*=14.4, 9.5; N(O)S-HC**H**-CHOH), 4.66 (1H, m; C**H**-OH), 7.09 (1H, s; C**H**-Br), 7.22 (2H, m; C**H** Aromatic), 7.28-7.35 (5H, m; C**H** Aromatic), 7.85 (2H, m; C**H** Tosyl).

δ_C (125 MHz, $CDCl_3$): 21.6 (**C**H_3), 42.6 (**C**H_2-Ph), 52.1 (Br-**C**H-Br), 54.1 (**C**H_2-CHOH), 67.4 (**C**H-OH), 126.7, 127.4, 128.9, 129.5 (**C**H Aromatic), 135.4 (**C** Phenyl), 139.5 (**C**-SO_2 Tosyl), 143.6 (CH_3-**C** Tosyl).

m/z (ESI): 171 (36), 410 (37), 523/525/527 (M, 48/100/48%).

Minor isomer **187**m

Rf: 0.35 (EtOAc/PE 20/80).

δ_H (500 MHz, $CDCl_3$): 2.41 (3H, s; C**H**$_3$), 2.71 (1H, d *J*=3.8; O**H**), 2.87 (1H, dd *J*=13.8, 8.0; Ph-**H**CH-CHOH), 2.91 (1H, dd *J*=13.7, 5.2; Ph-HC**H**-CHOH), 3.81 (1H, dd *J*=14.4, 9.5; N(O)S-**H**CH-CHOH), 4.04 (1H, dd *J*=14.5, 2.1; N(O)S-HC**H**-CHOH), 4.56 (1H, m; C**H**-OH), 7.11 (1H, s; C**H**-Br), 7.20 (2H, m; C**H** Aromatic), 7.28 (3H, m; C**H** Aromatic), 7.34 (2H, m; C**H** Aromatic), 7.85 (2H, m; C**H** Tosyl).

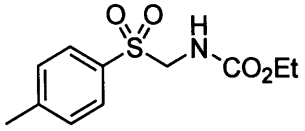
δ_C (125 MHz, $CDCl_3$): 21.5 (**C**H_3), 42.6 (**C**H_2-Ph), 51.0 (Br-**C**H-Br), 53.6 (N(O)S-**C**H_2-CHOH), 67.4 (**C**H-OH), 126.7, 127.4, 128.7, 129.5 (**C**H Aromatic), 135.5 (**C** Phenyl), 139.5 (**C**-SO_2 Tosyl), 143.5 (CH_3-**C** Tosyl).

m/z (FAB positive-methane): 154 (100), 219 (12), 273 (13), 289 (34), 307 (70), 524/526/528 (MH^+, 5/10/5%).

*IR (υ_{max} cm^{-1}, DCM cast, **187**):* 1080, 1153, 1305, 1319, 1454, 1498, 1599; 3474 (O-H).

4.2.4. Sulfones

Ethyl *N*-[(*p*-tolylsulfonyl)methyl]carbamate 151[203]



In a two-necked round-bottom flask fitted with a condenser, was dissolved sodium *p*-toluenesulfinate (17.8 g, 0.10 mol) in water (100 mL) and then were added successively urethane (10.7 g, 0.12 mol), formaldehyde aqueous solution (37% w/v, 10.0 mL, 0.14 mol) and formic acid (25 mL, 0.65 mol). The mixture was heated at 70 °C for 1h30; the mixture was allowed to cool to room temperature and then cooled in an ice bath for 2 hours The crude carbamate precipitate formed was collected by filtration, washed with cold water

(2x50 mL), dried under high vacuum pump at room temperature and used without any further purification (16.4 g, 64% yield).

Rf: 0.30 (EtOAc/PE 40/60).

δ_H *(400 MHz, $CDCl_3$):* 1.13 (3H, t *J*=7.1; CH_2-C**H**$_3$), 2.44 (3H, s; C**H**$_3$ Tosyl), 3.97 (2H, q *J*=7.1; O-C**H**$_2$-CH_3), 4.54 (2H, d *J*=7.0; O_2S-C**H**$_2$-NH), 5.48 (1H, t *J*=6.3; CH_2-N**H**), 7.35 (2H, d *J*=8.1; C**H** Tosyl), 7.79 (2H, d *J*=8.2; C**H** Tosyl).

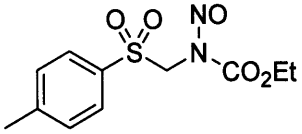
δ_C *(100 MHz, $CDCl_3$):* 14.3 (CH_2-**C**H_3), 21.7 (**C**H_3 Tosyl), 61.8 (**C**H_2-NH), 62.3 (O-**C**H_2-CH_3), 128.9, 129.8 (**C**H Tosyl), 133.7 (**C**-SO_2 Tosyl), 145.3 (CH_3-**C** Tosyl), 155.1 (**C**=O).

m/z (CI positive-methane): 102 (100), 139 (57), 185 (18), 258 (MH^+, 15%).

IR (υ_{max} cm^{-1}, DCM cast): 1032, 1251, 1300, 1537; 1690 (C=O); 2937; 3300 (NH).

Melting Point: 108-110 °C (lit. 108-110 °C).[203]

Ethyl *N*-nitroso-*N*-[(*p*-tolylsulfonyl)methyl]carbamate 152[164]



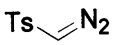
To a solution of carbamate **151** (5.0 g, 19 mmol) in dry DCM (50 mL), under argon atmosphere, were added successively dry pyridine (2.20 mL, 27 mmol), isoamylnitrite (3.65 mL, 27 mmol) and distilled chlorotrimethylsilane (6.95 mL, 54 mmol). The mixture was stirred at room temperature for 16 hours before DCM was added to bring the volume of the reaction mixture to 120 mL. The organic phase was washed with saturated sodium bicarbonate aqueous solution (2x50 mL), 1M hydrochloric acid (50 mL) and brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the crude product as a bright yellow powder. Recrystallisation from DCM/ether 1/2 afforded the pure nitroso derivative **152** in 76% yield (4.15 g).

Rf: 0.55 (EtOAc/PE 40/60).

δ_H *(400 MHz, $CDCl_3$):* 1.40 (3H, t *J*=7.1; CH_2-C**H**$_3$), 2.45 (3H, s; C**H**$_3$ Tolyl), 4.49 (2H, q *J*=7.1; O-C**H**$_2$-CH_3), 5.10 (2H, s; S-C**H**$_2$-NH), 7.35 (2H, d *J*=8.5; C**H** Tosyl), 7.79 (2H, dt *J*=8.3, 1.8; C**H** Tosyl).

δ_C (100 MHz, $CDCl_3$): 14.0 (CH_2-**C**H_3), 21.7 (**C**H_3 Tosyl), 58.2 (**C**H_2-N), 65.3 (O-**C**H_2-CH_3), 128.4, 130.0 (**C**H Tosyl), 134.9 (**C**-SO_2 Tosyl), 145.8 (CH_3-**C** Tosyl), 152.3 (**C**=O).
m/z (CI positive-methane): 102 (100), 139 (63), 287 (MH^+, 13%).
Melting Point: 89-90 °C (lit. 88-89 °C).[203]

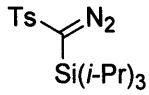
Tosyldiazomethane 153[164]



In a flask covered with foil, was suspended activated alumina (200 °C for 24 h., 10 g, 0.10 mol), in dry ether (30 mL) under argon atmosphere. In another flask was dissolved nitroso derivative **152** (1.0 g, 3.5 mmol) in dry DCM (3 mL) under argon atmosphere. The latter solution was poured into the alumina suspension and stirred for 16 hours at room temperature. The suspension was filtered and the silica was washed with DCM (3x50 mL), the filtrate was concentrated *in vacuo* to give tosyldiazomethane **153** as a orange-yellow oil that crystallises upon standing (0.54 g, 78% yield).

Rf: 0.40 (ether/PE 20/80).
δ_H (400 MHz, $CDCl_3$): 2.44 (3H, s; C**H**$_3$ Tolyl), 5.26 (1H, s; S-C**H**=N_2), 7.33 (2H, d *J*=8.0; C**H** Tosyl), 7.76 (2H, d *J*=8.4; C**H** Tosyl).
δ_C (100 MHz, $CDCl_3$): 21.6 (**C**H_3 Tosyl), 57.7 (**C**H=N_2), 126.3, 129.9 (**C**H Tosyl), 141.3 (**C**-SO_2 Tosyl), 144.3 (CH_3-**C** Tosyl).
m/z (CI positive-methane): 91 (100), 139 (10), 155 (Ts^+, 20%).
Melting Point: 35-38 °C (lit. 35-38 °C).[203]

Triisopropylsilyl-tosyl-diazomethane 192[204]



To a solution of tosyldiazomethane **153** (200 mg, 1.02 mmol) in dry ether (2.4 mL) at -78 °C was added dropwise successively distilled DIPEA (231 mL, 1.32 mmol) and TIPS triflate (404 mL, 1.32 mmol). The reaction mixture, allowed to warm to room temperature, was stirred for 16 hours then neutralized with Na_2CO_3, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica (PE, AcOEt/PE 2/98) to give silane **192** as bright yellow crystals (310 mg, 86% yield).

Recrystallisation from hexane gave bright yellow needles used for analysis purpose.

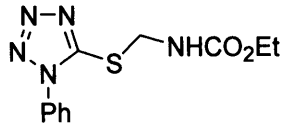
Rf: 0.35 (ether/PE 10/90).

δ_H (400 MHz, $CDCl_3$): 1.08 (18H, d *J*=7.4; 6x**CH_3** *i*-Pr), 1.32 (3H, m; 3x**CH** *i*-Pr), 2.44 (3H, s; **CH_3** Tolyl), 7.32 (2H, br dt *J*=8.6, 1.9; **CH** Tosyl), 7.75 (2H, dt *J*=8.4, 1.8; **CH** Tosyl).

δ_C (100 MHz, $CDCl_3$): 11.7 (**C**H *i*-Pr), 18.2 (**CH_3** *i*-Pr), 21.5 (**CH_3** Tosyl), 55.5 (**C**=N_2), 126.5, 129.6 (**C**H Tosyl), 141.3 (**C**-SO_2 Tosyl), 143.7 (CH_3-**C** Tosyl).

m/z (CI positive-methane): 131 (56), 157 (36), 171 (15), 283 (65), 309 (75), 353 (MH^+, 15%).

Ethyl *N*-[(1-phenyl)tetrazol-5-yl-sulfanylmethyl]carbamate



To a solution of tetrazole **205** (10.0 g, 56 mmol) in toluene (140 mL) were added successively urethane (5.0 g, 56 mmol), paraformaldehyde (2.2 g, 73 mmol) and 5 drops of piperidine. The mixture was heated under reflux for 18 hours with a Dean-Stark removal of water apparatus. The mixture was cooled to room temperature and then to -18 °C. The crude carbamate crystallised from cold toluene was collected by filtration, washed with cold toluene and used without any further purification (10.0 g, 64% yield). However, recrystallisation from ethanol 97% gave carbamate as white pellets.

Rf: 0.45 (EtOAc/PE 40/60).

δ_H (400 MHz, $CDCl_3$): 1.26 (3H, t *J*=6.8; **CH_3**-CH_2), 4.18 (2H, br q *J*=7.0; CH_3-**CH_2**), 5.73 (2H, d *J*=7.25; **CH_2**-NH), 6.23 (1H, br s; CH_2-N**H**), 7.49-7.56 (3H, m; **CH** Phenyl), 7.94 (2H, m; **CH** Phenyl).

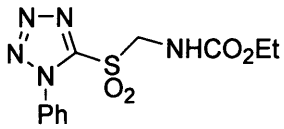
δ_C (100 MHz, $CDCl_3$): 14.3 (**CH_3**-CH_2), 54.1 (S-**CH_2**-N), 62.0 (CH_3-**CH_2**), 123.5, 129.2 (*o-/m-***C**H Phenyl), 129.6 (*p-***C**H Phenyl), 134.4 (**C** Phenyl), 155.7 (**C**=O), 163.2 (N-**C**(N)-S).

m/z (CI positive-methane): 119 (42), 179 (100), 280 (MH^+, 94%).

IR (υ_{max} cm^{-1}, DCM cast): 1022, 1230, 1498, 1510; 1732 (C=O); 3300 (N-H).

Melting Point: 136-137 °C (recrystallised front ethanol 97%).

Ethyl *N*-[(1-phenyl)tetrazol-5-yl-sulfonylmethyl) carbamate 206



To a solution of the corresponding sulfide (5.0 g, 18 mmol) and BTEAC (0.5 g, 2 mmol) in DCM (50 mL) was added water (100 mL) followed by potassium permanganate (14.1 g, 90 mmol). The mixture was stirred at room temperature for 24 hours. Water (100 mL) was added and the excess of oxidant reduced by adding sodium sulfite. Then ethyl acetate (300 mL) was added and the biphasic system was stirred at room temperature for 15 hours The two phases were separated and the organic phase was dried over sodium sulfate, filtered and the solvent evaporated *in vacuo*. Recrystallisation of the sulfone from the crude oil with cold ethanol 97% (7 mL, -18 °C) yielded the pure product **206** in 53% yield (1.19 g).

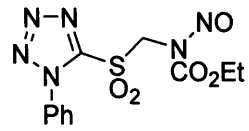
Rf: 0.20 (EtOAc/PE 40/60).

δ_H (400 MHz, $CDCl_3$): 1.24 (3H, t *J*=7.0; C**H**$_3$-CH$_2$), 4.18 (2H, br d *J*=6.9; CH$_3$-C**H**$_2$), 5.44 (2H, d *J*=6.9; C**H**$_2$-NH), 5.92 (1H, br s; CH$_2$-N**H**), 7.37 (1H, m; *p*-C**H** Phenyl), 7.49 (2H, m; *o-/m*-C**H** Phenyl), 7.91 (2H, m; *o-/m*-C**H** Phenyl).

δ_C (100 MHz, $CDCl_3$): 14.4 (**C**H$_3$-CH$_2$), 51.0 (S-**C**H$_2$-N), 61.8 (CH$_3$-**C**H$_2$), 119.2, 129.3 (*o-/m*-**C**H Phenyl), 127.8 (*p*-**C**H Phenyl), 134.3 (**C** Phenyl), 148.7 (N-**C**(N)-S), 155.8 (**C**=O).

IR (υ_{max} cm^{-1}, DCM cast): 690, 758, 1026, 1134, 1246; 1383 (SO_2); 1504, 1599; 1732 (C=O); 3331 (N-H).

Ethyl *N*-nitroso-*N*-[(1-phenyl)tetrazol-5-yl-sulfonylmethyl) carbamate 207[164]



To a solution of carbamate **206** (1.0 g, 3.2 mmol) in dry DCM (10 mL), under argon atmosphere, were added successively pyridine (0.79 mL, 9.9 mmol), isoamylnitrite (1.30 mL, 9.6 mmol) and chlorotrimethylsilane (2.46 mL, 19.2 mmol). The mixture was stirred at room temperature for 16 hours before DCM was added to bring the volume of the reaction mixture to 30 mL. The organic phase was washed with saturated sodium bicarbonate aqueous solution (2x20 mL), 1M hydrochloric acid (20 mL) and brine (20 mL), dried over

magnesium sulfate, filtered and concentrated *in vacuo* to give the crude product; recrystallisation from cold DCM/ether 1/2 (4 °C) afforded the pure nitroso derivative **207** in 90% yield (0.98 g).

Rf: 0.50 (EtOAc/PE 40/60).

δ_H *(400 MHz, $CDCl_3$):* 1.49 (3H, t *J*=7.2; C**H**$_3$-CH_2), 4.62 (2H, q *J*=7.2; CH_3-C**H**$_2$), 5.83 (2H, s; C**H**$_2$-NH), 7.37 (1H, m, *p*-C**H** Phenyl), 7.48 (2H, t *J*=8.3; *o-/m*-C**H** Phenyl), 7.88 (2H, dd *J*=8.8, 1.3; *o-/m*-C**H** Phenyl).

δ_C *(100 MHz, $CDCl_3$):* 14.2 (**C**H_3-CH_2), 45.4 (S-**C**H_2-N), 65.4 (CH_3-**C**H_2), 119.2, 129.4 (*o-/m*-**C**H Phenyl), 128.0 (*p*-**C**H Phenyl), 134.2 (**C** Phenyl), 147.7 (N-**C**(N)-S), 152.7 (**C**=O).

Melting Point: 65-67 °C

5. Appendix: X-Ray Structure of *t*-180e (str0488)

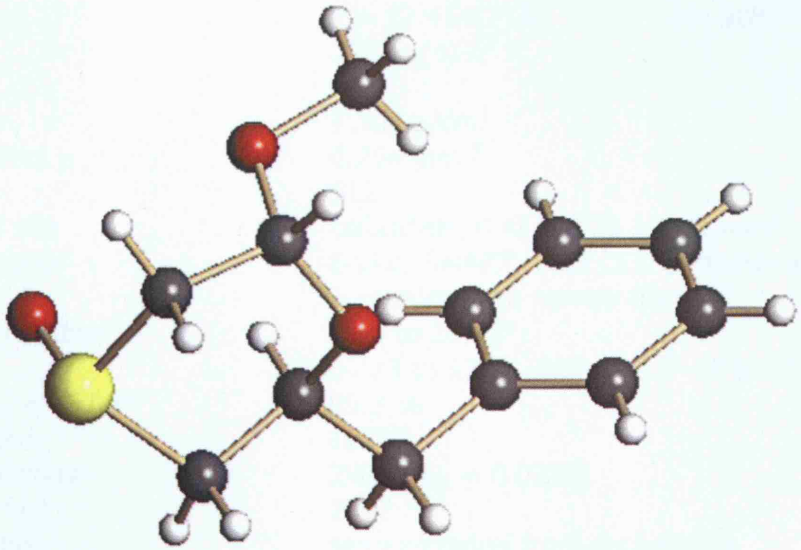


Table 1. Crystal data and structure refinement for str0488.

Identification code	str0488	
Chemical formula	$C_{12}H_{16}O_3S$	
Formula weight	240.31	
Temperature	298(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/n$	
Unit cell parameters	a = 10.6188(17) Å	α = 90°
	b = 9.5143(16) Å	β = 102.259(3)°
	c = 12.414(2) Å	γ = 90°
Cell volume	1225.6(4) Å^3	
Z	4	
Calculated density	1.302 g/cm^3	
Absorption coefficient μ	0.254 mm^{-1}	
F(000)	512	
Crystal colour and size	colourless, 0.48 × 0.23 × 0.21 mm^3	
Data collection method	Bruker SMART APEX CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	2.30 to 28.23°	
Index ranges	h –13 to 13, k –11 to 12, l –16 to 16	
Completeness to θ = 26.00°	99.3 %	
Reflections collected	10387	
Independent reflections	2903 (R_{int} = 0.0228)	
Reflections with $F^2>2\sigma$	2397	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.8879 and 0.9486	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0699, 0.1894	
Data / restraints / parameters	2903 / 0 / 145	
Final R indices [$F^2>2\sigma$]	R1 = 0.0420, wR2 = 0.1161	
R indices (all data)	R1 = 0.0511, wR2 = 0.1230	
Goodness-of-fit on F^2	1.024	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.232 and –0.272 e Å^{-3}	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for str0488. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
S(1)	0.37812(4)	0.15186(5)	0.42248(4)	0.06060(17)
O(1)	0.08100(9)	0.09142(10)	0.39998(8)	0.0447(2)
O(2)	0.18390(11)	−0.12644(11)	0.40658(9)	0.0527(3)
O(3)	0.41252(11)	0.05069(13)	0.34195(11)	0.0684(3)
C(1)	−0.08545(19)	0.0264(2)	0.11254(14)	0.0679(5)
C(2)	−0.1874(2)	−0.0600(2)	0.06674(15)	0.0807(6)
C(3)	−0.3032(2)	−0.0467(2)	0.09936(16)	0.0762(6)
C(4)	−0.31567(18)	0.0483(2)	0.17862(18)	0.0712(5)
C(5)	−0.21318(16)	0.13559(16)	0.22410(16)	0.0596(4)
C(6)	−0.09746(15)	0.12696(16)	0.19004(12)	0.0501(4)
C(7)	0.01374(15)	0.22360(16)	0.23649(14)	0.0542(4)
C(8)	0.12685(13)	0.14898(14)	0.30892(11)	0.0432(3)
C(9)	0.23826(14)	0.24774(16)	0.35037(15)	0.0554(4)
C(10)	0.29650(15)	0.05907(19)	0.51415(13)	0.0584(4)
C(11)	0.16612(13)	−0.00479(16)	0.46511(11)	0.0465(3)
C(12)	0.06657(18)	−0.20220(19)	0.37137(15)	0.0643(4)

Table 3. Bond lengths [Å] and angles [°] for str0488.

S(1)–O(3)	1.4881(13)	S(1)–C(10)	1.8013(18)
S(1)–C(9)	1.8096(16)	O(1)–C(11)	1.4136(16)
O(1)–C(8)	1.4313(16)	O(2)–C(11)	1.4005(18)
O(2)–C(12)	1.425(2)	C(1)–C(2)	1.382(3)
C(1)–C(6)	1.382(2)	C(2)–C(3)	1.379(3)
C(3)–C(4)	1.364(3)	C(4)–C(5)	1.390(2)
C(5)–C(6)	1.384(2)	C(6)–C(7)	1.511(2)
C(7)–C(8)	1.5154(19)	C(8)–C(9)	1.513(2)
C(10)–C(11)	1.516(2)		

O(3)–S(1)–C(10)	109.09(8)	O(3)–S(1)–C(9)	106.65(8)
C(10)–S(1)–C(9)	96.03(8)	C(11)–O(1)–C(8)	114.59(10)
C(11)–O(2)–C(12)	111.82(12)	C(2)–C(1)–C(6)	121.20(19)
C(3)–C(2)–C(1)	119.61(19)	C(4)–C(3)–C(2)	120.14(18)
C(3)–C(4)–C(5)	120.10(19)	C(6)–C(5)–C(4)	120.65(18)
C(5)–C(6)–C(1)	118.22(16)	C(5)–C(6)–C(7)	121.32(15)
C(1)–C(6)–C(7)	120.46(15)	C(6)–C(7)–C(8)	113.45(12)
O(1)–C(8)–C(9)	109.97(12)	O(1)–C(8)–C(7)	106.75(11)
C(9)–C(8)–C(7)	112.02(12)	C(8)–C(9)–S(1)	110.83(10)
C(11)–C(10)–S(1)	117.62(11)	O(2)–C(11)–O(1)	112.25(10)
O(2)–C(11)–C(10)	109.10(12)	O(1)–C(11)–C(10)	112.87(13)

Table 4. Anisotropic displacement parameters ($Å^2$) for str0488. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	0.0359(2)	0.0651(3)	0.0802(3)	–0.0114(2)	0.01116(18)	–0.00456(15)
O(1)	0.0366(5)	0.0531(5)	0.0454(5)	0.0020(4)	0.0113(4)	0.0026(4)
O(2)	0.0532(6)	0.0488(6)	0.0561(6)	0.0024(5)	0.0120(5)	0.0021(4)
O(3)	0.0526(6)	0.0737(8)	0.0845(8)	–0.0023(6)	0.0271(6)	0.0123(5)
C(1)	0.0674(11)	0.0868(13)	0.0504(8)	–0.0024(9)	0.0146(8)	–0.0056(9)
C(2)	0.0978(16)	0.0888(14)	0.0525(9)	–0.0113(9)	0.0094(10)	–0.0169(11)
C(3)	0.0730(12)	0.0786(13)	0.0678(11)	0.0110(10)	–0.0056(9)	–0.0201(10)
C(4)	0.0524(9)	0.0648(11)	0.0938(13)	0.0173(10)	0.0100(9)	–0.0001(8)
C(5)	0.0544(9)	0.0482(8)	0.0759(11)	0.0071(7)	0.0135(8)	0.0073(7)
C(6)	0.0515(8)	0.0477(8)	0.0481(7)	0.0149(6)	0.0040(6)	0.0047(6)
C(7)	0.0509(8)	0.0449(7)	0.0655(9)	0.0106(7)	0.0097(7)	0.0037(6)
C(8)	0.0416(7)	0.0406(7)	0.0496(7)	0.0003(5)	0.0146(6)	0.0016(5)
C(9)	0.0445(8)	0.0458(8)	0.0786(10)	–0.0035(7)	0.0191(7)	–0.0026(6)
C(10)	0.0442(8)	0.0772(11)	0.0503(8)	–0.0095(7)	0.0023(6)	0.0021(7)
C(11)	0.0428(7)	0.0570(8)	0.0396(6)	0.0013(6)	0.0083(5)	0.0035(6)
C(12)	0.0710(11)	0.0561(9)	0.0654(10)	0.0011(8)	0.0135(8)	–0.0122(8)

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for str0488.

	x	y	z	U
H(1A)	–0.0073	0.0166	0.0908	0.081
H(2A)	–0.1781	–0.1267	0.0142	0.097
H(3A)	–0.3728	–0.1027	0.0672	0.091
H(4A)	–0.3929	0.0548	0.2023	0.085
H(5A)	–0.2224	0.2004	0.2779	0.071
H(7A)	–0.0164	0.2968	0.2792	0.065
H(7B)	0.0428	0.2685	0.1759	0.065
H(8A)	0.1557	0.0725	0.2671	0.052
H(9A)	0.2132	0.3164	0.3997	0.066
H(9B)	0.2596	0.2978	0.2886	0.066
H(10A)	0.3527	–0.0158	0.5488	0.070
H(10B)	0.2855	0.1236	0.5720	0.070
H(11A)	0.1271	–0.0334	0.5265	0.056
H(12A)	0.0822	–0.2841	0.3309	0.096
H(12B)	0.0044	–0.1432	0.3249	0.096
H(12C)	0.0340	–0.2303	0.4346	0.096

Table 6. Torsion angles [°] for str0488.

C(6)–C(1)–C(2)–C(3)	–0.5(3)	C(1)–C(2)–C(3)–C(4)	–1.9(3)
C(2)–C(3)–C(4)–C(5)	2.2(3)	C(3)–C(4)–C(5)–C(6)	–0.2(3)
C(4)–C(5)–C(6)–C(1)	–2.1(2)	C(4)–C(5)–C(6)–C(7)	178.39(14)
C(2)–C(1)–C(6)–C(5)	2.5(2)	C(2)–C(1)–C(6)–C(7)	–178.00(16)
C(5)–C(6)–C(7)–C(8)	111.15(16)	C(1)–C(6)–C(7)–C(8)	–68.34(18)
C(11)–O(1)–C(8)–C(9)	–69.93(14)	C(11)–O(1)–C(8)–C(7)	168.35(11)
C(6)–C(7)–C(8)–O(1)	–61.78(16)	C(6)–C(7)–C(8)–C(9)	177.80(13)
O(1)–C(8)–C(9)–S(1)	68.36(13)	C(7)–C(8)–C(9)–S(1)	–173.10(11)
O(3)–S(1)–C(9)–C(8)	60.10(13)	C(10)–S(1)–C(9)–C(8)	–51.92(12)
O(3)–S(1)–C(10)–C(11)	–65.50(14)	C(9)–S(1)–C(10)–C(11)	44.46(14)
C(12)–O(2)–C(11)–O(1)	–62.27(15)	C(12)–O(2)–C(11)–C(10)	171.85(13)
C(8)–O(1)–C(11)–O(2)	–64.89(14)	C(8)–O(1)–C(11)–C(10)	58.91(15)
S(1)–C(10)–C(11)–O(2)	75.44(15)	S(1)–C(10)–C(11)–O(1)	–50.08(16)

6. References

1 M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**.

2 E. Galardon, P. L. Maux, L. Toupet, G. Simonneaux, *Organometallics* **1998**, *17*, 565.

3 M. Laabassi, R. Grée, *Tetrahedron Lett.* **1988**, *29*, 611.

4 M. Mikolajczyk, R. Zurawinski, P. Kielbasinski, *Tetrahedron Lett.* **1989**, *30*, 1143.

5 H. J. Monteiro, *Tetrahedron Lett.* **1987**, *28*, 3459.

6 M. P. Doyle, D. Van Leusen, *J. Org. Chem.* **1982**, *47*, 5326.

7 C. G. Venier, H. J. Barager, M. A. Ward, *J. Am. Chem. Soc.* **1975**, *97*, 3238.

8 D. H. Bremner, M. M. Campbell, *J. Chem. Soc., Chem. Com.* **1976**, 538.

9 A. R. Maguire, P. G. Kelleher, G. Ferguson, J. F. Gallagher, *Tetrahedron Lett.* **1998**, *39*, 2819.

10 E. Mellanby, *Brit. Med. J.* **1946**, *2*, 885.

11 P. N. Campbell, T. S. Work, E. Mellanby, *Biochem. J.* **1951**, *48*, 106.

12 H. R. Bentley, E. E. McDermott, J. Pace, J. K. Whitehead, T. Moran, *Nature* **1949**, *163*, 675.

13 H. R. Bentley, E. E. McDermott, J. Pace, J. K. Whitehead, T. Moran, *Nature* **1950**, *165*, 150.

14 H. R. Bentley, R. G. Booth, E. N. Greer, J. G. Heathcote, J. B. Hutchison, T. Moran, *Nature* **1948**, *161*, 126.

15 H. R. Bentley, J. K. Whitehead, *J. Chem. Soc.* **1950**, 2081.

16 M. Reggelin, C. Zur, *Synthesis* **2000**, *1*, 1.

17 T. Yoshimura, E. Tsukurimichi, H. Kita, H. Fujii, C. Shimasaki, *Tetrahedron Lett.* **1989**, *30*, 6339.

18 N. Furukawa, E. Horn, T. Yoshimura, T. Fujii, M. Ohkubo, S. Ono, H. Morita, E. R. T. Tiekink, *Z. Kristallogr.- New Cryst. Struct.* **1998**, *213*, 53.

19 C. R. Johnson, M. Haake, C. W. Schroeck, *J. Am. Chem. Soc.* **1970**, *92*, 6594.

20 C. R. Johnson, E. R. Janiga, *J. Am. Chem. Soc.* **1973**, *95*, 7692.

21 C. R. Johnson, R. A. Kirchhoff, R. J. Reischer, G. F. Katekar, *J. Am. Chem. Soc.* **1973**, *95*, 4287.

22 C. R. Johnson, C. W. Schroeck, *J. Am. Chem. Soc.* **1973**, *95*, 7418.

23 R. W. Heintzelman, D. Swern, *Synthesis* **1976**, 731.

24 H. Kwart, A. A. Khan, *J. Am. Chem. Soc.* **1967**, *89*, 1950.

25 C. R. Johnson, O. Lavergne, *J. Org. Chem.* **1989**, *54*, 986.

26 Y. Tamura, K. Sumoto, J. Minamikawa, M. Ikeda, *Tetrahedron Lett.* **1972**, *40*, 4137.

27 C. R. Johnson, R. A. Kirchhoff, H. G. Corkins, *J. Org. Chem.* **1974**, *39*, 2458.

28 N. Haga, Y. Endo, K. Kataoka, K. Yamaguchi, K. Shudo, *J. Am. Chem. Soc.* **1992**, *114*, 9795.

29 T. Bach, C. Körber, *Eur. J. Org. Chem.* **1999**, 1033.

30 T. Bach, C. Körber, *Tetrahedron Lett.* **1998**, *39*, 5015.

31 C. Bolm, K. Muñiz, N. Aguilar, M. Kesselgruber, G. Raabe, *Synthesis* **1999**, 1251.

32 O. G. Mancheno, C. Bolm, *Org. Lett.* **2006**, *8*, 2349.

33 J. T. Groves, T. Takahashi, *J. Am. Chem. Soc.* **1983**, *105*, 2073.
34 D. Mansuy, J.-P. Mahy, A. Dureault, G. Bedi, P. Battioni, *Chem. Commun.* **1984**, 1161.
35 D. A. Evans, M. M. Faul, M. T. Bilodeau, *J. Org. Chem.* **1991**, *56*, 6744.
36 Z. Li, K. R. Conser, E. N. Jacobsen, *J. Am. Chem. Soc.* **1993**, *115*, 5326.
37 H. Takada, Y. Nishibayashi, K. Ohe, S. Uemura, *Chem. Commun.* **1996**, *1996*, 931.
38 J. F. K. Muller, P. Vogt, *Tetrahedron Lett.* **1998**, *39*, 4805.
39 P. Dauban, R. H. Dodd, *J. Org. Chem.* **1999**, *64*, 5304.
40 S. Cren, T. C. Kinahan, C. L. Skinner, H. Tye, *Tetrahedron Lett.* **2002**, *43*, 2749.
41 C. Bolm, M. Kesselgruber, K. Muniz, G. Raabe, *Organometallics* **2000**, *19*, 1648.
42 M. J. Södergen, D. A. Alonso, A. V. Bedekar, P. G. Andersson, *Tetrahedron Lett.* **1997**, *38*, 6897.
43 J. Nakayama, T. Otani, Y. Sugihara, Y. Sano, A. Ishii, A. Sakamoto, *Heteroatom Chemistry* **2001**, *12*, 333.
44 D. Leca, K. Song, M. Amatore, L. Fensterbank, E. Lacôte, M. Malacria, *Chem. Eur. J.* **2004**, *10*, 906.
45 S. Taylor, J. Gullick, P. McMorn, D. Bethell, P. C. Bulman Page, F. E. Hancock, F. King, G. J. Hutchings, *J. Chem. Soc., Perkin Trans. 2* **2001**, *2*, 1714.
46 H. Okamura, C. Bolm, *Org. Lett.* **2004**, *6*, 1305.
47 G. Y. Cho, C. Bolm, *Org. Lett.* **2005**, *7*, 4983.
48 Y. Cui, C. He, *J. Am. Chem. Soc.* **2003**, *125*, 16202.
49 Y. Cui, C. He, *Angew. Chem. Int. Ed.* **2004**, *43*, 4210.
50 T. Siu, A. K. Yudin, *J. Am. Chem. Soc.* **2002**, *124*, 530.
51 T. Siu, A. K. Yudin, *Org. Lett.* **2002**, *4*, 1839.
52 L. B. Krasnova, R. M. Hili, O. V. Chernoloz, A. K. Yudin, *Arkivoc* **2005**, *iv*.
53 T. Siu, C. J. Picard, A. K. Yudin, *J. Org. Chem.* **2005**, *70*, 932.
54 G. Y. Cho, C. Bolm, *Tetrahedron Lett.* **2005**, *46*, 8007.
55 H. S. Raper, **1917**.
56 F. G. Mann, W. J. Pope, *J. Chem. Soc.* **1922**, *121*, 1052.
57 J. Holloway, J. Kenyon, H. Phillips, *J. Chem. Soc.* **1928**, 3000.
58 D. S. Tarbell, C. Weaver, *J. Am. Chem. Soc.* **1941**, *63*, 2939.
59 Y. Tamura, J. Minamikawa, M. Ikeda, *Synthesis* **1977**, 1.
60 P. K. Claus, W. Rieder, P. Hofbauer, E. Vilsmaier, *Tetrahedron* **1975**, *31*, 505.
61 D. J. Cram, J. Day, D. R. Rayner, D. M. V. Schriltz, D. J. Duchamp, D. C. Garwood, *J. Am. Chem. Soc.* **1970**, *92*, 7369.
62 R. Annunziata, M. Cinquini, F. Cozzi, *J. Chem. Soc., Perkin Trans. 1* **1981**, 1109.
63 C. R. Johnson, D. McCants, *J. Am. Chem. Soc.* **1965**, *87*, 5404.
64 J. Day, D. J. Cram, *J. Am. Chem. Soc.* **1965**, *87*, 4398.
65 H. Takada, Y. Nishibayashi, K. Ohe, S. Uemura, C. P. Baird, T. J. Sparey, P. C. Taylor, *J. Org. Chem.* **1997**, *62*, 6512.
66 P. S. Aujla, C. P. Baird, P. C. Taylor, H. Mauger, Y. Vallee, *Tetrahedron Lett.* **1997**, *38*, 7453.
67 Z. Li, R. W. Quan, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5889.
68 A. L. Marzinzik, K. B. Sharpless, *J. Org. Chem.* **2001**, *66*, 594.

69 I. Jalsovszky, F. Ruff, M. Kajtar-Peredy, I. Kövesdi, A. Kucsman, *Tetrahedron* **1986**, *42*, 5649.
70 H. Nishikori, C. Ohta, E. Oberlin, R. Irie, T. Katsuki, *Tetrahedron* **1999**, *55*, 13937.
71 H. Nishikori, T. Katsuki, *Tetrahedron Lett.* **1996**, *37*, 9245.
72 C. Kokubo, T. Katsuki, *Tetrahedron* **1996**, *52*, 13895.
73 R. Irie, K. Masutani, T. Katsuki, *Synlett* **2000**, 1433.
74 M. Murakami, T. Uchida, T. Katsuki, *Tetrahedron Lett.* **2001**, *42*, 7071.
75 Y. Tamura, T. Uchida, T. Katsuki, *Tetrahedron Lett.* **2003**, *44*, 3301.
76 J. G. Moffatt, U. Lerch, *J. Org. Chem.* **1971**, *36*, 3391.
77 C. R. Johnson, J. J. Rigau, *J. Org. Chem.* **1968**, *33*, 4340.
78 H. R. Bentley, J. K. Whitehead, *J. Chem. Soc.* **1952**, 1572.
79 P. Stoss, G. Satzinger, *Tetrahedron Lett.* **1973**, 1974.
80 T. Yoshimura, T. Omata, N. Furukawa, S. Oae, *J. Org. Chem.* **1976**, *41*, 1728.
81 H. S. Veale, J. Levin, D. Swern, *Tetrahedron Lett.* **1978**, 503.
82 C. R. Johnson, R. A. Kirchhoff, *J. Org. Chem.* **1979**, *44*, 2280.
83 S.-L. Huang, D. Swern, *J. Org. Chem.* **1979**, *44*, 2510.
84 K. Akutagawa, N. Furukawa, S. Oae, *J. Org. Chem.* **1984**, *49*, 2282.
85 D. M. Ketcha, D. Swern, *Synth. Commun.* **1984**, *14*, 915.
86 C. R. Johnson, C. W. Schroeck, J. R. Shanklin, *J. Am. Chem. Soc.* **1973**, *95*, 7424.
87 C. R. Johnson, O. Lavergne, *J. Org. Chem.* **1993**, *58*, 1922.
88 C. Bolm, C. Hackenberger, O. Simi, M. Verrucci, D. Müller, F. Bienewald, *Synthesis* **2002**, 879.
89 H. C. Brown, P. Heim, *J. Org. Chem.* **1973**, *38*, 912.
90 C. Bolm, F. Bienewald, H. Harms, *Synlett* **1996**, 775.
91 C. Bolm, O. Simic, M. Martin, *Synlett* **2001**, 1878.
92 C. Bolm, G. Moll, Jan D. Kahmann, *Chem. Eur. J.* **2001**, *7*, 1118.
93 J. R. Dehli, C. Bolm, *J. Org. Chem.* **2004**, *69*, 8518.
94 M. C. Willis, G. N. Brace, *Tetrahedron Lett.* **2002**, *43*, 9085.
95 D. J. Wallace, D. J. Klauber, C. y. Chen, R. P. Volante, *Org. Lett.* **2003**, *5*, 4749.
96 Juan R. Dehli, C. Bolm, *Adv. Synth. Catal.* **2005**, *347*, 239.
97 A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1995**, *34*, 1348.
98 J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609.
99 R. W. Heintzelman, R. B. Bailey, D. Swern, *J. Org. Chem.* **1976**, *41*, 2207.
100 C. R. Johnson, K. G. Bis, J. H. Cantillo, N. A. Meanwell, M. F. D. Reinhard, J. R. Zeller, G. P. Vonk, *J. Org. Chem.* **1983**, *48*, 1.
101 M. Harmata, *Tetrahedron Lett.* **1989**, *30*, 437.
102 C. Bolm, J. P. Hildebrand, *J. Org. Chem.* **2000**, *65*, 169.
103 S. Wagaw, R. A. Rennels, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 8451.
104 C. Bolm, J. P. Hildebrand, J. Rudolph, *Synthesis* **2000**, 911.
105 J. P. Wolfe, J. Ahman, J. P. Sadighi, R. A. Singer, S. L. Buchwald, *Tetrahedron Lett.* **1997**, *38*, 6367.
106 M. Rottlander, P. Knochel, *J. Org. Chem.* **1998**, *63*, 203.
107 M. Harmata, X. Hong, S. K. Ghosh, *Tetrahedron Lett.* **2004**, *45*, 5233.

108 D. M. T. Chan, K. L. Monaco, R.-P. Wang, M. P. Winters, *Tetrahedron Lett.* **1998**, *39*, 2933.
109 D. A. Evans, J. L. Katz, T. R. West, *Tetrahedron Lett.* **1998**, *39*, 2937.
110 P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941.
111 K. Okano, H. Tokuyama, T. Fukuyama, *Org. Lett.* **2003**, *5*, 4987.
112 G. Xu, Y. G. Wang, *Org. Lett.* **2004**, *6*, 985.
113 G. Y. Cho, P. Rémy, J. Jansson, C. Moessner, C. Bolm, *Org. Lett.* **2004**, *6*, 3293.
114 P. Y. S. Lam, D. Bonne, G. Vincent, C. G. Clark, A. P. Combs, *Tetrahedron Lett.* **2003**, *44*, 1691.
115 J.-B. Lan, L. Chen, X.-Q. Yu, J.-S. You, R.-G. Xie, *Chem. Commun.* **2004**, 188.
116 J.-B. Lan, G.-L. Zhang, X.-Q. Yu, J.-S. You, L. Chen, M. Yan, R.-G. Xie, *Synlett* **2004**, 1095.
117 C. Moessner, C. Bolm, *Org. Lett.* **2005**, *7*, 2667.
118 J. Sedelmeier, C. Bolm, *J. Org. Chem.* **2005**, *70*, 6904.
119 C. R. Johnson, C. J. Stark, *Tetrahedron Lett.* **1979**, 4713.
120 C. Bolm, M. Felder, *Tetrahedron Lett.* **1993**, *34*, 6041.
121 C. Bolm, O. Simic, *J. Am. Chem. Soc.* **2001**, *123*, 3830.
122 C. R. Johnson, J. P. Lockard, E. R. Kennedy, *J. Org. Chem.* **1980**, *45*, 264.
123 D. Jerchel, L. Dippelhofer, D. Renner, *Chem. Ber.* **1954**, *87*, 947.
124 M. Reggelin, H. Weinberger, V. Spohr, *Adv. Synth. Catal.* **2004**, *346*, 1295.
125 M. Langner, P. Rémy, C. Bolm, *Chem. Eur. J.* **2005**, *11*, 6254.
126 H. Zollinger, *Diazo Chemistry II*, VCH Verlagsgesellschaft mbH, Weinheim, **1995**.
127 H. Zollinger, *Diazo Chemistry I*, VCH Verlagsgesellschaft mbH, Weinheim, **1994**.
128 W. v. E. Doering, C. H. DePuy, *J. Am. Chem. Soc.* **1953**, *75*, 5955.
129 M. Regitz, A. Liedhegeher, *Chem. Ber.* **1966**, *99*, 3128.
130 M. Regitz, *Angew. Chem. Int. Ed.* **1966**, *5*, 681.
131 T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091.
132 A. M. Van Leusen, J. Strating, *Quart. Rep. Sulfur Chem.* **1967**, *5*, 67.
133 M. Regitz, W. Bartz, *Chem. Ber.* **1970**, *103*, 1477.
134 H. Balli, F. Kersting, *Liebigs Ann. Chem.* **1961**, *1*, 647.
135 H. Balli, *Angew. Chem. Int. Ed.* **1970**, *9*, 80.
136 H. Balli, R. Löw, V. Müller, H. Rempler, A. Sezen-Gezgin, *Helv. Chim. Acta* **1978**, *61*, 97.
137 H. J. Monteiro, *Synth. Commun.* **1987**, *17*, 983.
138 A. B. Charette, R. P. Wurz, T. Ollevier, *J. Org. Chem.* **2000**, *65*, 9252.
139 R. P. Wurz, W. Lin, A. B. Charette, *Tetrahedron Lett.* **2003**, *44*, 8845.
140 D. A. Evans, T. C. Britton, *J. Am. Chem. Soc.* **1987**, *109*, 6881.
141 R. L. Danheiser, R. F. Miller, R. G. Brisbois, S. Z. Park, *J. Org. Chem.* **1990**, *55*, 1959.
142 D. F. Taber, D. M. Gleave, R. J. Herr, K. Moody, M. J. Hennessy, *J. Org. Chem.* **1995**, *60*, 2283.
143 S. Ghosh, I. Datta, *Synth. Commun.* **1991**, *21*, 191.
144 A. M. Van Leusen, B. A. Reith, D. Van Leusen, *Tetrahedron* **1975**, 597.
145 A. Padwa, Z. J. Zhang, L. Zhi, *J. Org. Chem.* **2000**, *65*, 5223.

146 N. A. Swain, R. C. D. Brown, G. Bruton, *Chem. Commun.* **2002**, *2002*, 2042.
147 N. A. Swain, R. C. D. Brown, G. Bruton, *J. Org. Chem.* **2004**, *69*, 122.
148 G. M. Green, N. P. Peet, W. A. Metz, *J. Org. Chem.* **2001**, *66*, 2509.
149 R. L. Rosati, L. V. Kapili, P. Morrissey, J. A. Retsema, *J. Med. Chem.* **1990**, *33*, 291.
150 O. C. M. O'Sullivan, S. G. Collins, A. R. Maguire, M. Böhm, W. Sander, *Eur. J. Org. Chem.* **2006**, *2006*, 2918.
151 I. Kuwajima, Y. Highuchi, H. Iwasawa, T. Sato, *Chem. Lett.* **1976**, 1271.
152 M. Hrytsak, N. Etkin, T. Durst, *Tetrahedron Lett.* **1986**, *27*, 5679.
153 S. D. Babu, M. Hrytsak, T. Durst, *Can. J. Chem.* **1989**, *67*, 1071.
154 S. Sengupta, S. Mondal, *Tetrahedron Lett.* **2003**, *44*, 6405.
155 M. Honma, M. Nakada, *Tetrahedron Lett.* **2003**, *44*, 9007.
156 H. Takeda, H. Watanabe, M. Nakada, *Tetrahedron* **2006**, *62*, 8054.
157 D. G. Melillio, I. Shinkai, T. Liu, K. Ryan, M. Sletzinger, *Tetrahedron Lett.* **1980**, *21*, 2783.
158 J. Brennan, I. L. Pinto, *Tetrahedron Lett.* **1983**, *24*, 4731.
159 C. R. Johnson, C. J. Stark, *J. Org. Chem.* **1982**, *47*, 1193.
160 H. M. L. Davies, N. J. S. Huby, W. R. Cantrell, J. L. Olive, *J. Am. Chem. Soc.* **1993**, *115*, 9468.
161 C. R. Johnson, H. G. Corkins, *J. Org. Chem.* **1978**, *43*, 4140.
162 C. R. Johnson, H. G. Corkins, *J. Org. Chem.* **1978**, *43*, 4136.
163 N. E. Searle, *Org. Syn.* **1963**, *Coll. Vol. 4*, 424.
164 C. Plessis, D. Uguen, A. De Cian, J. Fischer, *Tetrahedron Lett.* **2000**, *41*, 5489.
165 P. J. Stang, V. V. Zhdankin, *Chem. Rev.* **1996**, *96*, 1123.
166 V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523.
167 P. Muller, *Acc. Chem. Res.* **2004**, *37*, 243.
168 D. J. Fairfax, D. J. Austin, S. L. Xu, A. Padwa, *J. Chem. Soc., Perkin Trans. 1* **1992**, *1992*, 2837.
169 P. Dauban, L. Sanière, A. Tarrade, R. H. Dodd, *J. Am. Chem. Soc.* **2001**, *123*, 7707.
170 P. Muller, A. Ghanem, *Org. Lett.* **2004**, *6*, 4347.
171 R. P. Wurz, A. B. Charette, *J. Org. Chem.* **2004**, *69*, 1262.
172 B. Moreau, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 18014.
173 J. L. Garcia Ruano, M. C. Martinez, J. H. Rodriguez, E. M. Olefirowicz, E. L. Eliel, *J. Org. Chem.* **1992**, *57*, 4215.
174 Y. Horiguchi, E. Nakamura, I. Kuwajima, *Org. Syn.* **1996**, *73*, 123.
175 J. K. Koskimies, *Acta Chem. Scand.* **1984**, *B38*, 101.
176 D. G. Smith, *J. Chem. Soc., Perkin Trans. 1* **1990**, 3187.
177 G. K. Packard, Y. Hu, A. Vescovi, S. D. Rychnovsky, *Angew. Chem. Int. Ed.* **2004**, *43*, 2822.
178 A. R. Daniewski, P. M. Wovkulich, M. R. Uskokovic, *J. Org. Chem.* **1992**, *57*, 7133.
179 A. M. Misske, H. M. R. Hoffmann, *Tetrahedron* **1999**, *55*, 4315.
180 K. Bowden, I. M. Heilbron, E. R. H. Jones, B. C. L. Weedon, *J. Chem. Soc* **1946**, *1946*, 39.
181 J. Meinwald, J. Crandall, W. E. Hymans, *Org. Syn.* **1973**, *45*, 77.
182 L. Barbieri, V. Costantino, E. Fattorusso, A. Mangoni, E. Aru, S. Parapini, D. Taramelli, *Eur. J. Org. Chem.* **2004**, *2004*, 468.

183 J. D. White, U. M. Grether, C.-S. Lee, *Org. Syn.* **2005**, *82*, 108.
184 D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.
185 A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974.
186 K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651.
187 B. G. Davis, R. J. Nash, A. A. Watson, C. Smith, G. W. J. Fleet, *Tetrahedron* **1999**, *55*, 4501.
188 M. Ioannou, M. J. Porter, F. Saez, *Tetrahedron* **2005**, *61*, 43.
189 M. Ioannou, M. J. Porter, F. Saez, *Chem. Commun.* **2002**, *2002*, 346.
190 G. S. Nandra, P. S. Pang, M. J. Porter, J. M. Elliott, *Org. Lett.* **2005**, *7*, 3453.
191 H. Emde, G. Simchen, *Liebigs Ann. Chem.* **1983**, 816.
192 T. Allspach, H. Gümbel, M. Regitz, *J. Organomet. Chem.* **1985**, *290*, 33.
193 D. Seyferth, R. S. Marmor, P. Hilbert, *J. Org. Chem.* **1971**, *36*, 1379.
194 E. W. Colvin, B. J. Hamill, *J. Chem. Soc., Perkin Trans. 1* **1977**, 869.
195 D. G. Brown, E. J. Velthuisen, J. R. Commerford, R. G. Brisbois, T. H. Hoye, *J. Org. Chem.* **1996**, *61*, 2540.
196 J. C. Gilbert, U. Weerasooriya, *J. Org. Chem.* **1979**, *44*, 4997.
197 J. C. Gilbert, U. Weerasooriya, *J. Org. Chem.* **1982**, *47*, 1837.
198 P. R. Blakemore, W. J. Cole, P. J. Kocieński, A. Morley, *Synlett* **1998**, 26.
199 P. R. Blakemore, *J. Chem. Soc., Perkin Trans. 1* **2002**, *2002*, 2563.
200 A. K. Ghosh, A. Bischoff, J. Cappiello, *Eur. J. Org. Chem.* **2003**, *2003*, 821.
201 S. G. Pyne, Z. Dong, *J. Org. Chem.* **1996**, *61*, 5517.
202 L. A. Paquette, J. H. Barrett, *Org. Syn.* **1969**, *49*, 62.
203 A. M. Van Leusen, J. Strating, *Org. Synth.* **1977**, *57*, 95.
204 P. Müller, F. Lacrampe, G. Bernardinelli, *Tetrahedron: Asymmetry* **2003**, *14*, 1503.